(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 December 2000 (21.12.2000)

PCT

(10) International Publication Number
WO 00/76518 A1

(51) International Patent Classification⁷: A61K 31/4745, 31/437, C07D 471/02

(21) International Application Number: PCT/US00/15656

(22) International Filing Date: 8 June 2000 (08.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/138,365 10 June 1999 (10.06.1999) US
09/589,236 7 June 2000 (07.06.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR (utility model), KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/76518 A1

(54) Title: UREA SUBSTITUTED IMIDAZOQUINOLINES

(57) Abstract: Imidazoquinoline and tetrahydroimidazoquinoline compounds that contain urea, thiourea, acylurea, or sulfonylurea functionality at the 1-position are useful as immune response modifiers. The compounds and compositions of the invention can induce the biosynthesis of various cytokines and are useful in the treatment of a variety of conditions including viral diseases and neoplastic diseases.

Urea Substituted Imidazoquinolines

Field of the Invention

This invention relates to imidazoquinoline compounds that have a substituent at the 1-position containing urea, thiourea, acylurea or sulfonylurea functionality, to pharmaceutical compositions containing such compounds, and to pharmaceutical compositions containing imidazoquinoline compounds that have carbamate functionality at the 1-position. A further aspect of this invention relates to the use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals, and in the treatment of diseases, including viral and neoplastic diseases.

Background of the Invention

The first reliable report on the 1*H*-imidazo[4,5-*c*]quinoline ring system, Backman et al., J. Org. Chem. 15, 1278-1284 (1950) describes the synthesis of 1-(6-methoxy-8-quinolinyl)-2-methyl-1*H*-imidazo[4,5-*c*]quinoline for possible use as an antimalarial agent. Subsequently, syntheses of various substituted 1*H*-imidazo[4,5-*c*] quinolines were reported. For example, Jain et al., J. Med. Chem. 11, pp. 87-92 (1968), synthesized the compound 1-[2-(4-piperidyl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline as a possible anticonvulsant and cardiovascular agent. Also, Baranov et al., Chem. Abs. 85, 94362 (1976), have reported several 2-oxoimidazo[4,5-*c*]quinolines, and Berenyi et al., J. Heterocyclic Chem. 18, 1537-1540 (1981), have reported certain 2-oxoimidazo[4,5-c]quinolines.

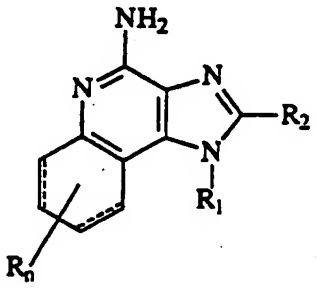
Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines and 1- and 2-substituted derivatives thereof were later found to be useful as antiviral agents, bronchodilators and immunomodulators. These are described in, *inter alia*, U.S. Patent Nos. 4,689,338; 4,698,348; 4,929,624; 5,037,986; 5,268,376; 5,346,905; and 5,389,640, all of which are incorporated herein by reference.

There continues to be interest in the imidazoquinoline ring system. For example, EP 894 797 describes imidazoquinoline type compounds that bear an amide containing substituent at the 1- position. The specification of this patent teaches that the active compounds of this series require a terminal amine substituent that may be incorporated into a heterocyclic ring. As another example, WO 00/09506 describes imidazopyridine

and imidazoquinoline compounds that may have an amide or urea containing substituent at the 1-position. The compounds described in this publication as having utility contain a 1-substituent wherein the amide or urea nitrogen is part of a heterocyclic ring. Despite these attempts to identify compounds that are useful as immune response modifiers, there is a continuing need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other mechanisms.

Summary of the Invention

We have found compounds that are useful in inducing cytokine biosynthesis in animals. Accordingly, this invention provides imidazoquinoline and tetrahydroimidazoquinoline compounds of Formula (I):



(I)

wherein R_1, R_2, and R are as defined *infra*. The invention also provides pharmaceutical compositions containing compounds of formula (Ia), which compounds have the same general structural formula as compounds (I) above.

The compounds of Formulae (I) and (Ia) are useful as immune response modifiers due to their ability to induce cytokine biosynthesis and otherwise modulate the immune response when administered to animals. This makes the compounds useful in the treatment of a variety of conditions, e.g. viral diseases and tumors that are responsive to such changes in the immune response.

The invention further provides pharmaceutical compositions that contain a therapeutically effective amount of a compound of Formula (I) or Ia), methods of inducing cytokine biosynthesis in an animal, treating a viral infection in an animal, and/or treating a

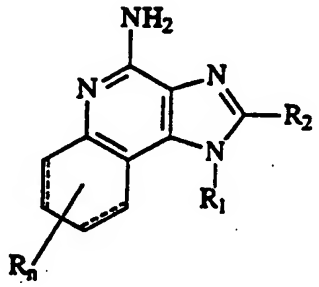
neoplastic disease in an animal by administering a compound of Formula (I) or (Ia) to the animal.

In addition, methods of synthesizing the compounds of the invention and intermediates useful in the synthesis of these compounds are provided.

Detailed Description of the Invention

As mentioned earlier, we have found that certain compounds induce cytokine biosynthesis in animals. Such compounds are represented by Formulae (I) and (Ia) below.

The invention provides compounds of Formula (I):



(I)

wherein

R_1 is -alkyl-NR_3-CY-NR_5-X-R_4 or -alkenyl-NR_3-CY- NR_5-X- R_4 wherein

Y is =O or =S;

X is a bond, -CO- or $-SO_2-$;

R_4 is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of:

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-substituted aryl;

-substituted heteroaryl;

-substituted heterocyclyl;

-O-alkyl;

-O-(alkyl)$_{0-1}$-aryl;

-O-(alkyl)$_{0-1}$-substituted aryl;

-O-(alkyl)$_{0-1}$-heteroaryl;

-O-(alkyl)$_{0-1}$-substituted heteroaryl;

-O-(alkyl)$_{0-1}$-heterocyclyl;

-O-(alkyl)$_{0-1}$-substituted heterocyclyl;

-COOH;

-CO-O-alkyl;

-CO-alkyl;

-S(O)$_{0-2}$-alkyl;

-S(O)$_{0-2}$–(alkyl)$_{0-1}$-aryl;

-S(O)$_{0-2}$–(alkyl)$_{0-1}$-substituted aryl;

-S(O)$_{0-2}$–(alkyl)$_{0-1}$-heteroaryl;

-S(O)$_{0-2}$–(alkyl)$_{0-1}$-substituted heteroaryl;

-S(O)$_{0-2}$–(alkyl)$_{0-1}$-heterocyclyl;

-S(O)$_{0-2}$–(alkyl)$_{0-1}$-substituted heterocyclyl;

-(alkyl)$_{0-1}$-NR_3R_3;

-(alkyl)$_{0-1}$-NR_3-CO-O-alkyl;

-(alkyl)$_{0-1}$-NR_3-CO-alkyl;

-(alkyl)$_{0-1}$-NR_3-CO-aryl;

-(alkyl)$_{0-1}$-NR_3-CO-substituted aryl;

-(alkyl)$_{0-1}$-NR_3-CO-heteroaryl;

-(alkyl)$_{0-1}$-NR_3-CO-substituted heteroaryl;

-N_3;

-halogen;

-haloalkyl;

-haloalkoxy;

-CO-haloalkoxy;

-NO_2;

-CN;

-OH; and

-SH; and in the case of alkyl, alkenyl, or heterocyclyl, oxo;

with the proviso that when X is a bond R_4 can additionally be hydrogen;

R_2 is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

- alkyl -O-alkyl;

-alkyl-O- alkenyl; and

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

$-N(R_3)_2$;

$-CO-N(R_3)_2$;

$-CO-C_{1-10}$ alkyl;

$-CO-O-C_{1-10}$ alkyl;

$-N_3$;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-heterocyclyl;

-substituted heterocyclyl;

-CO-aryl;

-CO-(substituted aryl);

-CO-heteroaryl; and

-CO-(substituted heteroaryl);

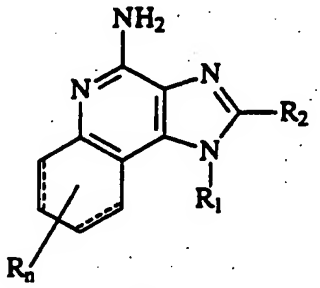
each R_3 is independently selected from the group consisting of hydrogen and C_{1-10} alkyl;

R_5 is selected from the group consisting of hydrogen and C_{1-10} alkyl, or R_4 and R_5 can combine to form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;

n is 0 to 4 and each R present is independently selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkoxy, halogen and trifluoromethyl,

or a pharmaceutically acceptable salt thereof.

The invention also provides pharmaceutical compositions comprising a therapeutically effective amount of a compound of Formula (Ia):



(Ia)

wherein

R_1 is -alkyl-NR_3-CO-O-R_4 or -alkenyl-NR_3-CO- O- R_4;

R_4 is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of:

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-substituted aryl;
-substituted heteroaryl;
-substituted heterocyclyl;
-O-alkyl;
-O-(alkyl)$_{0-1}$-aryl;
-O-(alkyl)$_{0-1}$-substituted aryl;
-O-(alkyl)$_{0-1}$-heteroaryl;
-O-(alkyl)$_{0-1}$-substituted heteroaryl;
-O-(alkyl)$_{0-1}$-heterocyclyl;
-O-(alkyl)$_{0-1}$-substituted heterocyclyl;
-COOH;
-CO-O-alkyl;
-CO-alkyl;
-S(O)$_{0-2}$-alkyl;
-S(O)$_{0-2}$-(alkyl)$_{0-1}$-aryl;
-S(O)$_{0-2}$-(alkyl)$_{0-1}$-substituted aryl;
-S(O)$_{0-2}$-(alkyl)$_{0-1}$-heteroaryl;
-S(O)$_{0-2}$-(alkyl)$_{0-1}$-substituted heteroaryl;
-S(O)$_{0-2}$-(alkyl)$_{0-1}$-heterocyclyl;
-S(O)$_{0-2}$-(alkyl)$_{0-1}$-substituted heterocyclyl;
-(alkyl)$_{0-1}$-NR_3R_3;
-(alkyl)$_{0-1}$-NR_3-CO-O-alkyl;
-(alkyl)$_{0-1}$-NR_3-CO-alkyl;
-(alkyl)$_{0-1}$-NR_3-CO-aryl;
-(alkyl)$_{0-1}$-NR_3-CO-substituted aryl;
-(alkyl)$_{0-1}$-NR_3-CO-heteroaryl;
-(alkyl)$_{0-1}$-NR_3-CO-substituted heteroaryl;
-N_3;
-halogen;
-haloalkyl;
-haloalkoxy;
-CO-haloalkoxy;

-NO_2;

-CN;

-OH; and

-SH; and in the case of alkyl, alkenyl, or heterocyclyl, oxo;

R_2 is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

- alkyl -O-alkyl;

-alkyl-O- alkenyl; and

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

-$N(R_3)_2$;

-CO-$N(R_3)_2$;

-CO-C_{1-10} alkyl;

-CO-O-C_{1-10} alkyl;

-N_3;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-heterocyclyl;

-substituted heterocyclyl;

-CO-aryl;

-CO-(substituted aryl);

-CO-heteroaryl; and

-CO-(substituted heteroaryl);

each R_3 is independently selected from the group consisting of hydrogen and C_{1-10} alkyl;

n is 0 to 4 and each R present is independently selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkoxy, halogen and trifluoromethyl,

or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

Preparation of the Compounds

Imidazoquinolines of the invention can be prepared according to Reaction Scheme I where R, R_1, R_2 and n are as defined above.

In step (1) of Reaction Scheme I a 4-chloro-3-nitroquinoline of Formula II is reacted with an amine of Formula R_1NH_2 where R_1 is as defined above to provide a 3-nitroquinolin-4-amine of Formula III. The reaction can be carried out by adding amine to a solution of a compound of Formula II in a suitable solvent such as chloroform or dichloromethane and optionally heating. Many quinolines of Formula II are known compounds (see for example, U.S. Patent 4,689,338 and references cited therein).

In step (2) of Reaction Scheme I a 3-nitroquinolin-4-amine of Formula III is reduced to provide a quinoline-3,4-diamine of Formula IV. Preferably, the reduction is carried out using a conventional heterogeneous hydrogentation catalyst such as platinum on carbon or palladium on carbon. The reaction can conveniently be carried out on a Parr apparatus in a suitable solvent such as isopropyl alcohol or toluene.

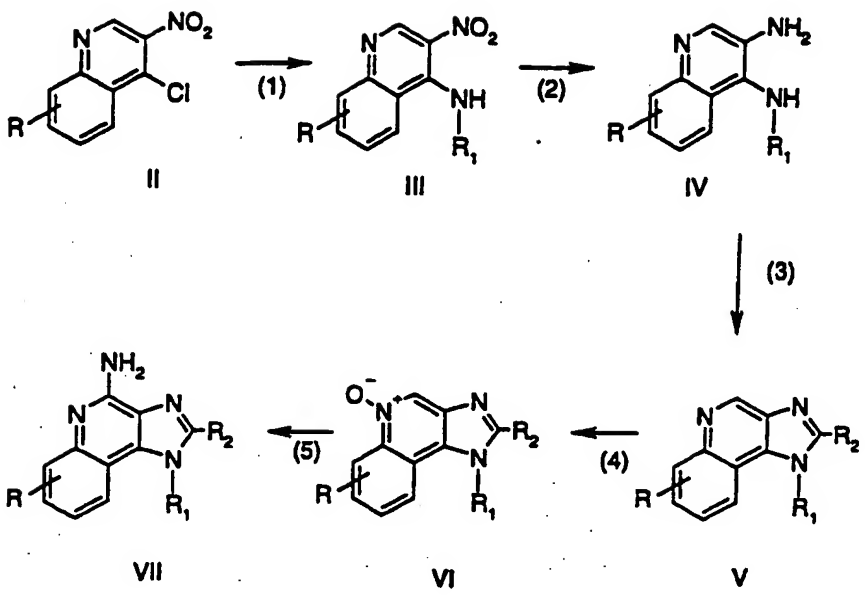
In step (3) of Reaction Scheme I a quinoline-3,4-diamine of Formula IV is reacted with a carboxylic acid or an equivalent thereof to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula V. Suitable equivalents to carboxylic acid include acid halides, orthoesters, and 1,1-dialkoxyalkyl alkanoates. The carboxylic acid or equivalent is selected such that it will provide the desired R_2 substituent in a compound of Formula V. For example, triethyl orthoformate will provide a compound where R_2 is hydrogen and triethyl orthoacetate will provide a compound where R_2 is methyl. The reaction can be run in the absence of solvent or in an inert solvent such as toluene. The reaction is run with sufficient heating to drive off any alcohol or water formed as a byproduct of the reaction.

In step (4) of Reaction Scheme I a 1*H*-imidazo[4,5-*c*]quinoline of Formula V is oxidized to provide a 1*H*-imidazo[4,5-*c*]quinoline-5N-oxide of Formula VI using a conventional oxidizing agent that is capable of forming N-oxides. Preferred reaction conditions involve reacting a solution of a compound of Formula V in chloroform with 3-chloroperoxybenzoic acid at ambient conditions.

In step (5) of Reaction Scheme I a 1*H*-imidazo[4,5-*c*]quinoline-5N-oxide of Formula VI is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula VII, which is a subgenus of Formula I. Step (5) involves (i) reacting a compound of Formula VI with an acylating agent and then (ii) reacting the product with an aminating agent. Part (i) of step (5) involves reacting an N-oxide of Formula VI with an acylating agent. Suitable acylating agents include alkyl- or arylsulfonyl chlorides (e.g., benezenesulfonyl chloride, methanesulfonyl chloride, p-toluenesulfonyl chloride). Arylsulfonyl chlorides are preferred. *Para*-toluenesulfonyl chloride is most preferred. Part (ii) of step (5) involves reacting the product of part (i) with an excess of an aminating agent. Suitable aminating agents include ammonia (e.g., in the form of ammonium hydroxide) and ammonium salts (e.g., ammonium carbonate, ammonium bicarbonate, ammonium phosphate). Ammonium hydroxide is preferred. The reaction is preferably carried out by dissolving the N-oxide of Formula VI in an inert solvent such as dichloromethane, adding the aminating agent to the solution, and then slowly adding the acylating agent. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Alternatively, step (5) may be carried out by (i) reacting an N-oxide of Formula VI with an isocyanate and then (ii) hydrolyzing the resulting product. Part (i) involves reacting the N-oxide with an isocyanate wherein the isocyanato group is bonded to a carbonyl group. Preferred isocyanates include trichloroacetyl isocyanante and aroyl isocyanates such as benzoyl isocyanate. The reaction of the isocyanate with the N-oxide is carried out under substantially anhydrous conditions by adding the isocyanate to a solution of the N-oxide in an inert solvent such as chloroform or dichloromethane. Part (ii) involves hydrolysis of the product from part (i). The hydrolysis can be carried out by conventional methods such as heating in the presence of water or a lower alkanol optionally in the presence of a catalyst such as an alkali metal hydroxide or lower alkoxide.

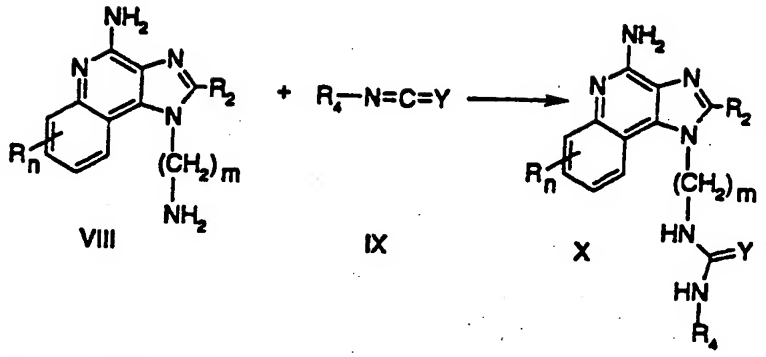
Reaction Scheme I



Compounds of the invention where the R_1 substituent contains a urea or a thiourea can also be prepared according to Reaction Scheme II where R, R_2, R_4 and n are as defined above and Y is O or S and m is an integer from 1 to 20.

In Reaction Scheme II an aminoalkyl substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula VIII is reacted with an isocyanate or thioisocyanate of Formula IX to provide a compound of Formula X which is a subgenus of Formula I. The reaction can be carried out by adding a solution of the (thio)isocyanate in a suitable solvent such as dichloromethane to a solution of a compound of Formula VIII, optionally at a reduced temperature. Many 1*H*-imidazo[4,5-*c*]quinolin-4-amines of Formula VIII are known compounds (see for example US 6,069,149 (Nanba)); others can be readily prepared using known synthetic methods. Many isocyanates and thioisocyanates of Formula IX are commercially available; others can be readily prepared using known synthetic methods. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

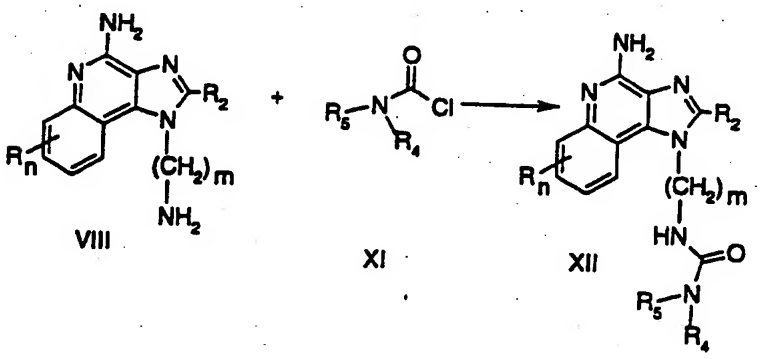
Reaction Scheme II



Compounds of the invention where the R_1 substituent contains a urea can also be prepared according to Reaction Scheme III where R, R_2, R_4, R_5 and n are as defined above and m is an integer from 1 to 20.

In Reaction Scheme III an aminoalkyl substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula VIII is reacted with a carbamoyl chloride of Formula XI to provide a compound of Formula XII which is a subgenus of Formula I. The reaction can be carried out by adding a solution of the carbamoyl chloride in a suitable solvent such as pyridine to a solution of a compound of Formula VIII at ambient temperature. Some carbamoyl chlorides of Formula XI are commercially available; others can be readily prepared using known synthetic methods. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme III

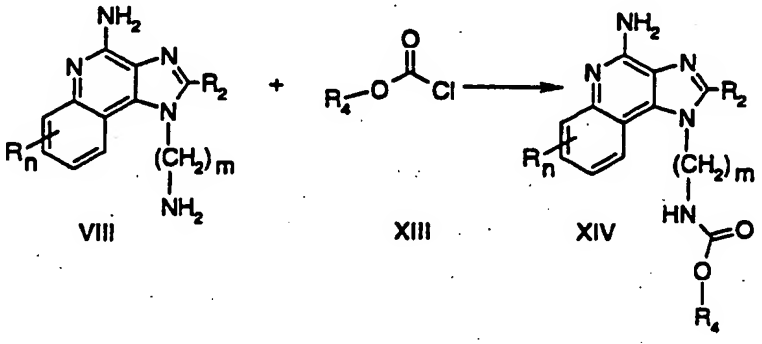


Compounds of the invention where the R_1 substituent contains a carbamate can also be prepared according to Reaction Scheme IV where R, R_2, R_4, n and m are as defined above.

In Reaction Scheme IV an aminoalkyl substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula VIII is reacted with an chloroformate of Formula XIII to provide a compound of Formula XIV which is a subgenus of Formula Ia. The reaction can be carried out by adding a solution of the chloroformate

in a suitable solvent such as dichloromethane or pyridine to a solution of a compound of Formula VIII optionally at a reduced temperature. Many chloroformates of Formula XIII are commercially available; others can be readily prepared using known synthetic methods. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

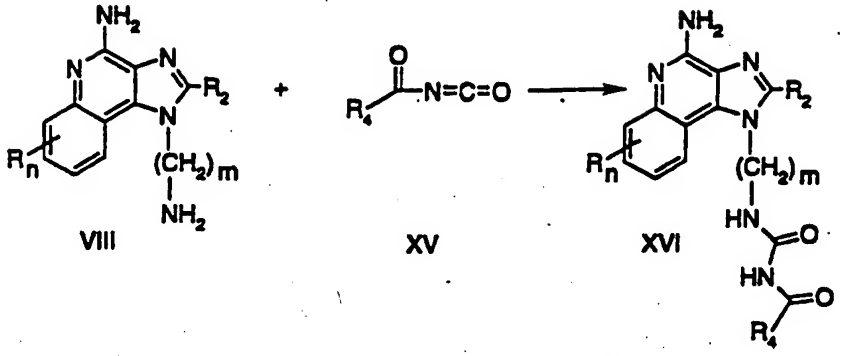
Reaction Scheme IV



Compounds of the invention where the R_1 substituent contains an acyl urea can also be prepared according to Reaction Scheme V where R, R_2, R_4, n and m are as defined above

In Reaction Scheme V an aminoalkyl substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula VIII is reacted with an acyl isocyanate of Formula XV to provide a compound of Formula XVI which is a subgenus of Formula I. The reaction can be carried out by adding a solution of the acyl isocyanate in a suitable solvent such as dichloromethane to a solution of a compound of Formula VIII at a reduced temperature. Some acyl isocyanates of Formula XV are commercially available; others can be readily prepared using known synthetic methods. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

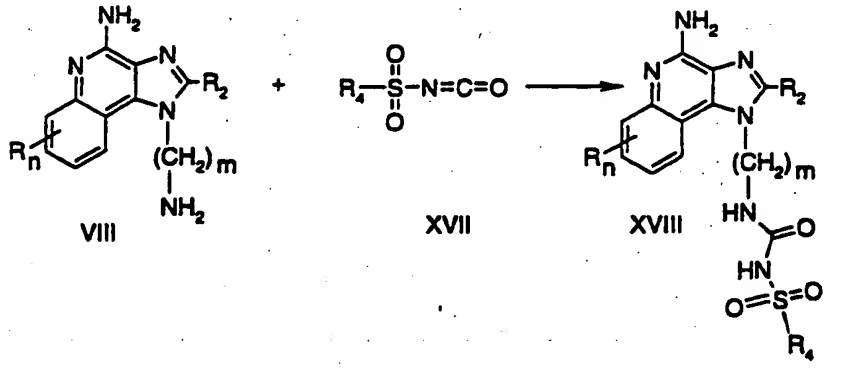
Reaction Scheme V



Compounds of the invention where the R_1 substituent contains a sulfonyl urea can also be prepared according to Reaction Scheme VI where R, R_2, R_4, n and m are as defined above

In Reaction Scheme VI an aminoalkyl substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula VIII is reacted with a sulfonyl isocyanate of Formula XVII to provide a compound of Formula XVIII which is a subgenus of Formula I. The reaction can be carried out by adding a solution of the sulfonyl isocyanate in a suitable solvent such as dichloromethane to a solution of a compound of Formula VIII, optionally at a reduced temperature. Some sulfonyl isocyanates of Formula XVII are commercially available; others can be readily prepared using known synthetic methods. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme VI

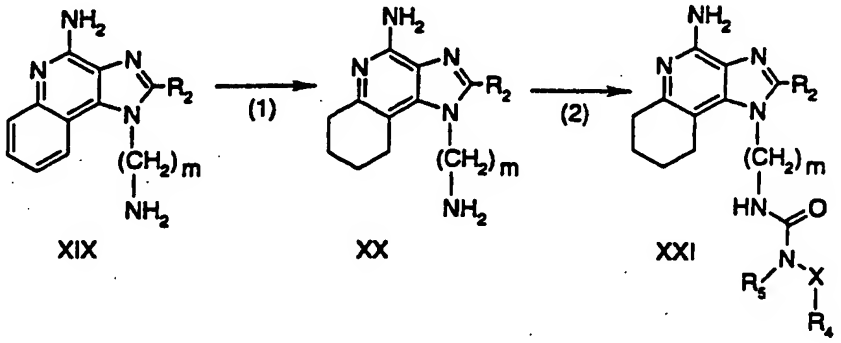


Tetrahydroimidazoquinolines of the invention can be prepared according to Reaction Scheme VII where R_2, R_3, R_4, R_5, X, Y and m are as defined above.

In step (1) of Reaction Scheme VII an aminoalkyl substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XIX is reduced to provide an aminoalkyl substituted 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XX. Preferably the reduction is carried out by suspending or dissolving the compound of Formula XIX in trifluoroacetic acid, adding a catalytic amount of platinum (IV) oxide, and then subjecting the mixture to hydrogen pressure. The reaction can conveniently be carried out on a Parr apparatus. The product or a salt thereof can be isolated using conventional methods.

Step (2) of Reaction Scheme VII can be carried out using the methods described in Reaction Schemes II, III, IV, V and VI to provide a compound of Formula XXI which is a subgenus of Formula I.

Reaction Scheme VII



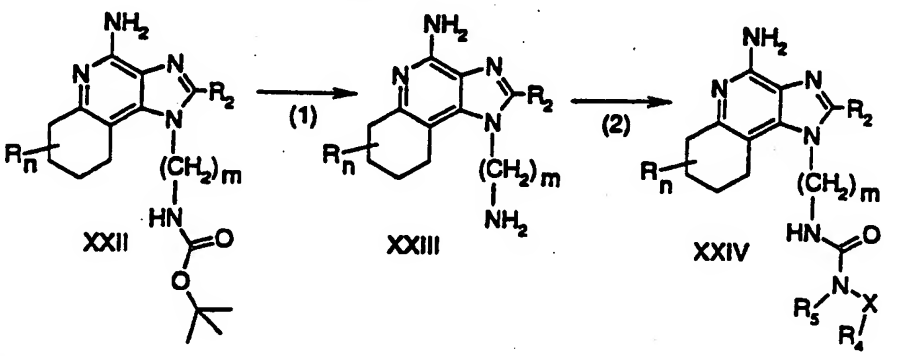
XIX XX XXI

Tetrahydroimidazoquinolines of the invention can also be prepared according to Reaction Scheme VIII where R, R_2, R_3, R_4, R_5, X, Y, n and m are as defined above.

In step (1) of Reaction Scheme VIII a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolinyl *tert*-butylcarbamate of Formula XXII is hydrolyzed to provide an aminoalkyl substituted 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXIII. The reaction can be carried out by dissolving the compound of Formula XXII in a mixture of trifluoroacetic acid and acetonitrile and stirring at ambient temperature. Alternatively, the compound of Formula XXII can be combined with dilute hydrochloric acid and heated on a steam bath. Tetrahydro-1*H*-imidazo[4,5-*c*]quinolinyl *tert*-butylcarbamates of Formula XXII can be prepared using the synthetic route disclosed in U.S. Patent 5,352,784 (Nikolaides). The product or a salt thereof can be isolated using conventional methods.

Step (2) of Reaction Scheme VIII can be carried out using the methods described in Reaction Schemes II, III, IV, V and VI to provide a compound of Formula XXIV which is a subgenus of Formula I.

Reaction Scheme VIII



Some compounds of Formula I can be readily prepared from other compounds of Formula I. For example, compounds wherein the R_4 substituent contains a chloroalkyl group can be reacted with an amine to provide an R_4 substituent substituted by a secondary or teriary amino group; compounds wherein the R_4 substituent contains a nitro group can be reduced to provide a compound wherein the R_4 substituent contains a primary amine.

As used herein, the terms "alkyl", "alkenyl", "alkynyl" and the prefix "-alk" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl and alkynyl groups containing from 2 to 20 carbon atoms. Preferred groups have a total of up to 10 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopentyl, cyclohexyl and adamantyl.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including groups wherein all of the available hydrogen atoms are replaced by halogen atoms. This is also true of groups that include the prefix "haloalk-". Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl. The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring

hetero atom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, tetrazolyl, imidazo, pyrazolo, oxazolo, thiazolo and the like.

"Heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring hetero atom (e.g., O, S, N). Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperdinyl, piperazinyl, thiazolidinyl, imidazolidinyl and the like.

Unless otherwise specified, the terms "substituted aryl", "substituted heteroaryl" and "substituted heterocyclyl" indicate that the rings or ring systems in question are further substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, hydroxy, halogen, haloalkyl, haloalkylcarbonyl, haloalkoxy (e.g., trifluoromethoxy), nitro, alkylcarbonyl, alkenylcarbonyl, arylcarbonyl, heteroarylcarbonyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocycloalkyl, nitrile, alkoxycarbonyl, alkanoyloxy, alkanoylthio, and in the case of heterocyclyl, oxo.

In structural formulas representing compounds of the invention certain bonds are represented by dashed lines. These lines mean that the bonds represented by the dashed line can be present or absent. Accordingly, compounds of Formula I can be either imidazoquinoline compounds or tetrahydroimidazoquinoline compounds.

The invention is inclusive of the compounds described herein in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and enantiomers, salts, solvates, polymorphs, and the like.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound of the invention in combination with a pharmaceutically acceptable carrier.

The term "a therapeutically effective amount" means an amount of the compound sufficient to induce a therapeutic effect, such as cytokine induction, antitumor activity and/or antiviral activity. Although the exact amount of active compound used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound as well as the nature of the carrier and the intended dosing regimen, it is anticipated that the

compositions of the invention will contain sufficient active ingredient to provide a dose of about 100ng/kg to about 50mg/kg, preferably about 10μg/kg to about 5mg/kg, of the compound to the subject. Any of the conventional dosage forms may be used, such as tablets, lozenges, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

The compounds of the invention can be administered as the single therapeutic agent in a treatment regimen, or the compounds of the invention may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, and so on.

The compounds of the invention have been shown to induce the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds are useful as immune response modifiers that can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines that maybe induced by the administration of compounds according to the invention generally include interferon (IFN) and/or tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds of the invention include IFN-α, TNF-α, IL-1, 6, 10 and 12, and a variety of other cytokines. Among other effects, cytokines inhibit virus production and tumor cell growth, making the compounds useful in the treatment of tumors and viral diseases.

In addition to the ability to induce the production of cytokines, the compounds of the invention affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds may also activate macrophages, which in turn stimulates secretion of nitric oxide and the production of additional cytokines. Further, the compounds may cause proliferation and differentiation of B-lymphocytes.

Compounds of the invention also have an effect on the acquired immune response. For example, although there is not believed to be any direct effect on T cells or direct induction of T cell cytokines, the production of the T helper type 1 (Th1) cytokine IFN-γ is induced indirectly and the production of the T helper type 2 (Th2) cytokines IL-4, IL-5 and IL-13 are inhibited upon administration of the compounds. This activity means that the compounds are useful in the treatment of diseases where upregulation of the Th1

response and/or downregulation of the Th2 response is desired. In view of the ability of compounds of Formula Ia to inhibit the Th2 immune response, the compounds are expected to be useful in the treatment of conditions that are associate with overstimulation of a Th2 response such as atopic diseases, e.g., atopic dermatitis; asthma; allergy; allergic rhinitis; systemic lupus erythematosis; as a vaccine adjuvant for cell mediated immunity; and possibly as a treatment for recurrent fungal diseases, periodontitis and chlamydia.

The immune response modifying effects of the compounds make them useful in the treatment of a wide variety of conditions. Because of their ability to induce the production of cytokines such as IFN-α and/or TNF-α, and IL-12, the compounds are particularly useful in the treatment of viral diseases and tumors. This immunomodulating activity suggests that compounds of the invention are useful in treating diseases such as, but not limited to, viral diseases including genital warts; common warts; plantar warts; Hepatitis B; Hepatitis C; Herpes Simplex Type I and Type II; molluscum contagiosum; HIV; CMV; VZV; intraepithelial neoplasias such as cervical intraepithelial neoplasia; human papillomavirus (HPV) and associated neoplasias; fungal diseases, e.g. candida, aspergillus, and cryptococcal meningitis; neoplastic diseases, e.g., basal cell carcinoma, hairy cell leukemia, Kaposi's sarcoma, renal cell carcinoma, squamous cell carcinoma, myelogenous leukemia, multiple myeloma, melanoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, and other cancers; parasitic diseases, e.g. pneumocystis carnii, cryptosporidiosis, histoplasmosis, toxoplasmosis, trypanosome infection, and leishmaniasis; and bacterial infections, e.g., tuberculosis, and mycobacterium avium. Additional diseases or conditions that can be treated using the compounds of the invention include eczema; eosinophilia; essential thrombocythaemia; leprosy; multiple sclerosis; Ommen's syndrome; discoid lupus; Bowen's disease; Bowenoid papulosis; and to enhance or stimulate the healing of wounds, including chronic wounds.

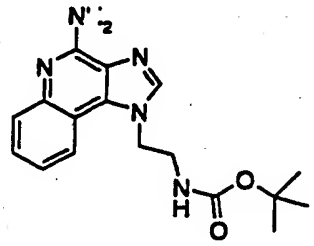
Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound of Formula Ia to the animal. An amount of a compound effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, TNF-α, IL-1,6,10 and 12 that is increased over the background level of such cytokines. The precise amount will vary according to factors known in the art but is

expected to be a dose of about 100ng/kg to about 50mg/kg, preferably about 10μg/kg to about 5mg/kg. The invention also provides a method of treating a viral infection in an animal comprising administering an effective amount of a compound of Formula Ia to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount will vary according to factors known in the art but is expected to be a dose of 100ng/kg to about 50mg/kg, preferably about 10μg/kg to about 5mg/kg. An amount effective to treat a neoplastic condition is an amount that will cause a reduction in tuor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 mg/kg to about 50 mg/kg. Preferably about 10 mg/kg to about 5 mg/kg.

The invention is further described by the following examples, which are provided for illustration only and are not intended to be limiting in any way.

Example 1

Tert-Butyl N-[2-(4-Amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate



Part A

Triethylamine (66.8 g, 0.33 mol) was added to a solution of *tert*-butyl N-(2-aminoethyl)carbamate (55.0 g, 0.34 mol) in anhydrous dichloromethane (500 mL). 4-Chloro-3-nitroquinoline (68.2 g, 0.33 mol) was slowly added and the reaction exothermed. The reaction mixture was allowed to stir at ambient temperature overnight. The resulting precipitate was isolated by filtration to provide product as a yellow solid. The filtrate was washed with water, dried over magnesium sulfate and then concentrated under vacuum. The resulting residue was slurried with hexane and filtered to provide additional product as a yellow solid. The two crops were combined to provide 101 g of *tert*-butyl N-[2-(3-nitroquinolin-4-yl)aminoethyl]carbamate as a yellow solid, m.p. 157-158.

Part B

Platinum on carbon (1 g of 10%) and sodium sulfate (2 g) were added to a slurry of *tert*-butyl N-[2-(3-nitroquinolin-4-yl)aminoethyl]carbamate (100 g, 0.30 mol) in toluene (500 mL). The mixture was placed under a hydrogen atmosphere at 50 psi (3.4×10^4 pascals) on a Parr apparatus at ambient temperature overnight. The reaction mixture was filtered. The filtrate was concentrated to provide 73 g of *tert*-butyl N-[2-(3-aminoquinolin-4-yl)aminoethyl]carbamate as a dark gold oil.

Part C

Triethyl orthoformate (11.3 g, 73.4 mmol) was added to a solution of *tert*-butyl N-[2-(3-aminoquinolin-4-yl)aminoethyl]carbamate (21 g, 69.4 mmol) in anhydrous toluene (250 mL). The reaction mixture was heated at reflux for 5 hours and then allowed to slowly cool to ambient temperature. The resulting precipitate was isolated by filtration and dried to provide 17.6 g of *tert*-butyl N-[2-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate as a light tan solid, m.p. 154-155°C.

Part D

3-Chloroperoxybenzoic acid (17.4 g, 60.6 mmol) was added in small portions to a solution of *tert*-butyl N-[2-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate (17.2 g, 55.1 mmol) in chloroform (250 mL). The reaction was maintained at ambient temperature overnight and then quenched with 5% sodium carbonate solution. The layers were separated. The organic layer was dried over magnesium sulfate and then concentrated under vacuum to provide 15.0 g of 1-[2-(*tert*-butylcarbamyl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline-5N-oxide as an off white solid, m.p. 213-215°C.

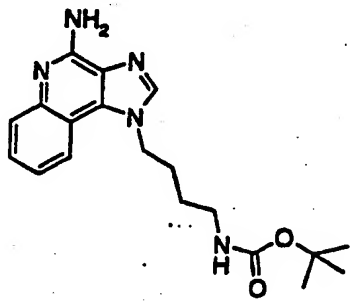
Part E

Trichloroacetyl isocyanate (9.5 g, 50.2 mmol) was slowly added to a stirred solution of 1-[2-(*tert*-butylcarbamyl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline-5N-oxide (15.0 g, 45.7 mmol) in chloroform (200 mL). After 2 hours the reaction was quenched with concentrated ammonium hydroxide (100 mL). Water (100 mL) was added and the layers were separated. The aqueous layer was extracted with chloroform. The organic layers were combined, dried over magnesium sulfate and then concentrated under vacuum to provide a white solid. This material was slurried in warm methyl acetate and then filtered to provide 15 g of *tert*-butyl N-[2-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate as a white solid, m.p. 215°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13 (t,

J=8.0 Hz, 1H), 8.03 (s, 1H), 7.61(d, J=8.0 Hz, 1H), 7.44 (t, J=8.0 Hz, 1H), 7.23 (t, J=8.0 Hz, 1H), 7.06 (t, J=6.0 Hz, 1H), 6.56 (broad s, 2H), 4.63 (t, J=7.0 Hz, 2H), 3.43 (q, J=6.0 Hz, 2H), 1.32 (s, 9H); MS (EI) m/e 327.1696 (327.1695 calcd for $C_{17}H_{21}N_5O_2$)

Example 2

Tert-Butyl N-[2-(4-Amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]carbamate



Part A

Using the general method of Example 1 Part A, *tert*-butyl N-(4-aminobutyl)carbamate (254 g, 1.35 mol) was reacted with 4-chloro-3-nitroquinoline hydrochloride (331 g, 1.35 mmol) to provide 486 g of *tert*-butyl N-(4-[(3-nitroquinolin-4-yl)amino]butyl)carbamate as yellow solid. Analysis: Calculated for $C_{18}H_{24}N_4O_4$: %C, 59.99; %H, 6.71; %N, 15.55; Found: %C, 59.68; %H, 6.59; %N, 15.74.

Part B

Using the general method of Example 1 Part B, *tert*-butyl N-(4-[(3-nitroquinolin-4-yl)amino]butyl)carbamate (162.6 g, 0.451 mol) was hydrogenated to provide 149 g of *tert*-butyl N-(4-[(3-aminoquinolin-4-yl)amino]butyl)carbamate as a dark gold gum.

Part C

Using the general method of Example 1 Part C, *tert*-butyl N-(4-[(3-aminoquinolin-4-yl)amino]butyl)carbamate (149 g, 0.451 mol) was reacted with triethyl orthoformate to provide crude product. This material was recrystallized from isopropyl alcohol to provide 84 g of *tert*-butyl N-[4-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]carbamate as a crystalline solid.

Part D

Using the general method of Example 1 Part D, *tert*-butyl N-[4-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]carbamate (84.0 g, 0.247 mol) was oxidized to provide 87.9 g of 1-

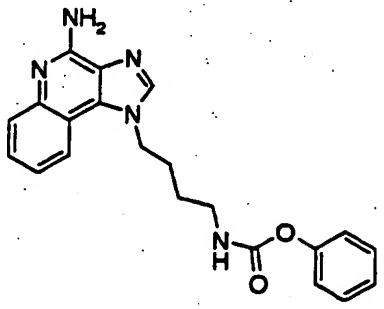
[4-(*tert*-butylcarbamyl)butyl]-1*H*-imidazo[4,5-*c*]quinoline-5N-oxide as a green/yellow foam.

Part E

Concentrated ammonium hydroxide (250 mL) was added to a vigorously stirred solution of 1-[4-(*tert*-butylcarbamyl)butyl]-1*H*-imidazo[4,5-*c*]quinoline-5N-oxide (87.9 g, 0.247 mol) in dichloromethane (750 mL). Tosyl chloride (47.0 g, 0.247 mol) was added in small portions over a period of 30 minutes. The reaction mixture was allowed to stir at ambient temperature overnight then it was filtered to remove a tan precipitate. The filtrate layers were separated. The aqueous layer was extracted with dichloromethane (4 x 50 mL). The dichloromethane fractions were combined, dried over sodium sulfate and then concentrated under vacuum to provide a pale tan solid. This material was recrystallized from isopropyl alcohol to provide 75.7 g of *tert*-butyl N-[2-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]carbamate as a pale yellow solid, m.p. 171-173°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.03 (d, J=8.0 Hz, 1H), 7.62 (d, J=8.0 Hz, 1H), 7.44 (t, J=8.0 Hz, 1H), 7.26 (d, J=8.0 Hz, 1H), 6.83 (t, J=6.0 Hz, 1H), 6.60 (broad s, 2H), 4.59 (t, J=7.0 Hz, 2H), 2.95 (q, J=6.0 Hz, 2H), 1.83 (quintet, J=7.0 Hz, 2H), 1.42 (quintet, J=7.0 Hz, 2H), 1.33 (s, 9H). MS (EI) m/e 355.2001 (355.2008 calcd for $C_{19}H_{25}N_5O_2$).

Example 3

Phenyl N-[4-(4-amino-1*H*-imidazo[4,5-c]quinolin-1-yl)butyl]carbamate

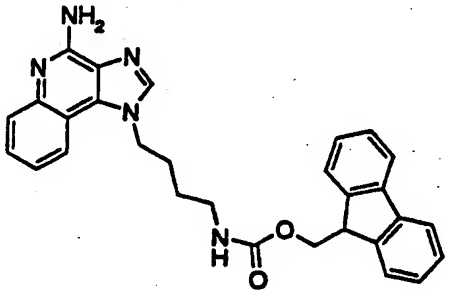


A solution of 1-(4-aminobutyl)-1*H*-imidazo[4,5-c]quinolin-4-amine (9.3 mg, 36 µmol) in 10 mL of dichloromethane was cooled to -5°C and a solution of phenyl chloroformate (7 mg, 45 µmol) in 1.5 mL of dichloromethane was added, with argon bubbling to facilitate mixing. The mixture was then allowed to warm to room temp. while being vortexed for 10 min. Aminomethylpolystyrene (ca. 80 mg, 1 meq/g, 100-200 mesh,

Bachem) was added to quench excess chloroformate, and the mixture was refluxed and vortexed for several hours. The mixture was chromatographed through a short plug of silica gel with 10:1 dichloromethane-methanol as eluant to isolate the product as a solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.28 (s, 1H), 8.06 (d, J=7.6 Hz, 1H), 7.76 (t, J=5.6 Hz, 1H), 7.63 (d, J=8.2 Hz, 1H), 7.45 (t, J=7 Hz, 1H), 7.34 (t, J=8.2 Hz, 2H), 7.27 (t, J=7.5 Hz, 1H), 7.18 (t, J=7.3 Hz, 1H), 7.00 (d, J=8.6 Hz, 2H), 6.65 (bs, 2H), 4.64 (t, J=7 Hz, 2H), 3.10 (q, J=6 Hz, 2H), 1.92 (quintet, J=7 Hz, 2H), 1.52 (quintet, J=7 Hz, 2H). MS (APCI) m/e 376.15 (M+H).

Example 4

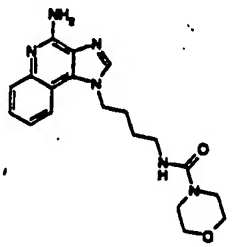
9*H*-9-Fluorenylmethyl N-[4-(4-amino-1*H*-imidazo[4,5-c]quinolin-1-yl)butyl]carbamate



To a solution of 1-(4-aminobutyl)-1*H*-imidazo[4,5-c]quinolin-4-amine (9.3 mg, 36 µmol) in 10 mL of dichloromethane at ambient temperature was added 9-fluorenylmethyl chloroformate (8 mg, 30 µmol) as a solid. The mixture was vortexed at room temperature for about 1 min., becoming slightly cloudy. Aminomethylpolystyrene (ca. 90 mg, 0.64 meq/g, 100-200 mesh, Bachem) was added to quench excess chloroformate, and after a few minutes the mixture was filtered through a short plug of silica gel, eluting with 10:1 dichloromethane-methanol to isolate the product as a solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (s, 1H), 8.08 (d, J=8.1 Hz, 1H), 7.87 (d, J=7.6 Hz, 2H), 7.65 (m, 3H), 7.50 (t, J=7.6 Hz, 1H), 7.40 (t, J=7.3 Hz, 2H), 7.3 (m, 4H), 7.15 (bs, 2H), 4.62 (t, J=7 Hz, 2H), 4.27 (d, J=7 Hz, 2H), 4.17 (t, J=7 Hz, 1H), 3.03 (q, J=7 Hz, 2H), 1.84 (quintet, J=7 Hz, 2H), 1.45 (quintet, J=7 Hz, 2H). MS (APCI) m/e 478.28 (M+H).

Example 5

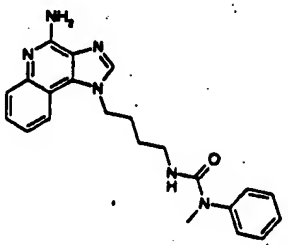
N^4-[4-(4-Amino-1*H*-imidazo[4,5-c]quinolin-1-yl)butyl]-4-morpholinecarboxamide



4-Morpholinecarbonyl chloride (0.15 ml, 1.3 mmol) was added to a stirring solution of 1-(4-aminobutyl)-1*H*-imidazo[4,5-c]quinolin-4-amine (0.3 g, 1.2 mmol) and pyridine (70 ml). The reaction was maintained at room temperature overnight. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, 9:1 dichloromethane\methanol). The fractions containing product were combined, washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), filtered, and concentrated to provide 0.86 g of N^4-[4-(4-amino-1*H*-imidazo[4,5-c]quinolin-1-yl)butyl]-4-morpholinecarboxamide as a tan powder, m.p. 177.0-179.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.22 (s, 1H), 8.04 (d, J=7.1 Hz, 1H), 7.64 (d, J=7.5 Hz, 1H), 7.47 (t, J=7.1 Hz, 1H), 7.28 (t, J=7.1 Hz, 1H), 6.72 (broad s, 2H), 6.52 (t, J=5.4 Hz, 1H), 4.61 (t, J=6.9 Hz, 2H), 3.48 (t J=4.6 Hz, 4H), 3.18 (t, J=4.6 Hz, 4H), 3.05 (m, 2H), 1.84 (m, 2H), 1.44 (m, 2H); MS (EI) m/e 368.1966 (368.1961 calcd for $C_{19}H_{24}N_6O_2$).

Example 6

N^1-[4-(4-Amino-1*H*-imidazo[4,5-c]quinolin-1-yl)butyl]-N-methyl-N-phenylurea

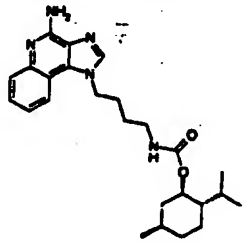


According to the general method of Example 5, 1-(4-aminobutyl)-1*H*-imidazo[4,5-c]quinolin-4-amine and N-methyl-N-phenylcarbamoyl chloride were

combined to provide N^1-[4-(4-amino-1*H*-imidazo[4,5-c]quinolin-1-yl)butyl]-N-methyl-N-phenylurea as a tan powder, m.p. 87.0-88.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.19 (s, 1H), 8.04 (d, J=8.1 Hz, 1H), 7.63 (dd, J=8.1, 1.2 Hz, 1H), 7.45 (dt, J=8.1, 1.2 Hz, 1H), 7.31-7.24 (m, 3H), 7.18-7.09 (m, 3H), 6.62 (s, 2H), 5.95 (broad s, 1H), 4.59 (t, J=6.9 Hz, 2H), 3.07 (s, 3H), 3.03 (m, 2H), 1.82 (quintet, J=7.2 Hz, 2H), 1.42 (quintet, J=7.2 Hz, 2H); MS (EI) m/e 388.2023 (388.2012 calcd for $C_{22}H_{24}N_6O$).

Example 7

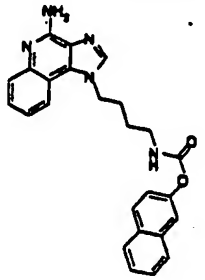
(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl N-[3-(4-amino-1*H*-imidazo[4,5-c]quinolin-1-yl)butyl]carbamate



(-)-Menthyl chloroformate (0.675 ml, 3.15 mmol) was added dropwise to a stirring solution of 1-(4-aminobutyl)-1*H*-imidazo[4,5-c]quinolin-4-amine (0.80 g, 3.14 mmol) and pyridine (200 ml). The reaction was maintained at room temperature overnight. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, 95:5 dichloromethane\methanol). The fractions containing product were combined, washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), filtered, and concentrated to provide 0.32 g of (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl N-[3-(4-amino-1*H*-imidazo[4,5-c]quinolin-1-yl)butyl]carbamate as a tan powder, m.p. 84.0-86.0 °C. ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.5, 152.5, 145.3, 143.1, 131.9, 128.5, 127.0, 126.5, 121.5, 120.8, 115.2, 73.0, 47.2, 46.5, 41.7, 34.1, 31.2, 27.5, 26.8, 26.1, 23.4, 22.3, 20.8, 16.6; MS (EI) m/e 437.2797 (437.2791 calcd for $C_{25}H_{35}N_5O_2$).

Example 8

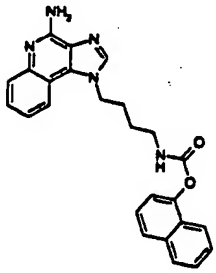
2-Naphthyl N-[4-(4-amino-1*H*-imidazo[4,5-c]quinolin-1-yl)butyl]carbamate



According to the general method of Example 7, 1-(4-aminobutyl)-1*H*-imidazo[4,5-c]quinolin-4-amine and chloroformic acid 2-naphthyl ester were combined to provide 2-naphthyl N-[4-(4-amino-1*H*-imidazo[4,5-c]quinolin-1-yl)butyl]carbamate as a white powder, m.p. 154.0-155.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.23 (s, 1H), 8.08 (d, J=7.4 Hz, 1H), 7.94-7.86 (m, 4H), 7.64 (dd, J=8.3, 1.0 Hz, 1H), 7.56-7.43 (m, 4H), 7.30 (m, 1H), 7.20 (dd, J=8.8, 2.3 Hz, 1H), 6.61 (broad s, 2H), 4.65 (t, J=6.9 Hz, 2H), 3.14 (q, J=6.4 Hz, 2H), 1.94 (m, 2H), 1.56 (m, 2H); MS (EI) m/e 426.1927 (426.1930 calcd for $C_{25}H_{23}N_5O_2$).

Example 9

1-Naphthyl N-[4-(4-amino-1*H*-imidazo[4,5-c]quinolin-1-yl)butyl]carbamate

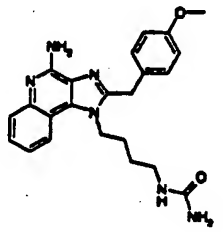


According to the general method of Example 7, 1-(4-aminobutyl)-1*H*-imidazo[4,5-c]quinolin-4-amine and chloroformic acid 1-naphthyl ester were combined to provide 1-naphthyl N-[4-(4-amino-1*H*-imidazo[4,5-c]quinolin-1-yl)butyl]carbamate as a tan powder, m.p. 89.0-92.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.25 (s, 1H), 8.10 (d, J=7.4 Hz, 1H), 8.05 (t, J=5.8 Hz, 1H), 7.96 (d, J=7.6 Hz, 1H), 7.79 (d, J=8.2 Hz, 1H), 7.66-7.45 (m, 6H), 7.30 (m, 1H), 7.19 (d, J=7.5 Hz, 1H), 6.72 (broad s, 2H), 4.67 (t, J=6.9

Hz, 2H), 3.17 (q, J=6.3 Hz, 2H), 1.96 (m, 2H), 1.59 (m, 2H); MS (EI) m/e 426.1929 (426.1930 calcd for $C_{25}H_{23}N_5O_2$).

Example 10

N-{4-[4-Amino-2-(4-methoxybenzyl)-1*H*-imidazo[4,5-c]quinolin-1-yl]butyl}urea



Part A

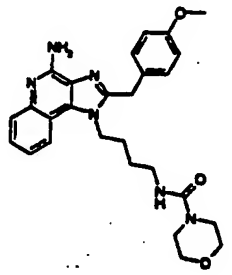
tert-Butyl N-{4-[2-(4-methoxybenzyl)-1*H*-imidazo[4,5-c]quinolin-1-yl]butyl}carbamate was reacted according to the general method of Example 1 parts D and E to provide *tert*-butyl N-aminocarbonyl-N-{4-[4-amino-2-(4-methoxybenzyl)-1*H*-imidazo[4,5-c]quinolin-1-yl]butyl}carbamate as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.93 (d, J=8.1 Hz, 1H), 7.86 (broad s, 1H), 7.61 (dd, J=8.3, 1.1 Hz, 1H), 7.41 (m, 1H), 7.24-7.17 (m, 4H), 6.87 (d, J=8.7 Hz, 2H), 6.55 (broad s, 2H), 4.45 (broad s, 2H), 4.32 (s, 2H), 3.71 (s, 3H), 3.49 (m, 2H), 1.49 (m, 4H), 1.31 (s, 9H).

Part B

The *tert*-butyl carbamoyl group was removed from *tert*-butyl N-aminocarbonyl-N-{4-[4-amino-2-(4-methoxybenzyl)-1*H*-imidazo[4,5-c]quinolin-1-yl]butyl}carbamate by heating the compound in a solution of HCl and ethanol. The reaction was neutralized (NH_4OH) to provide N-{4-[4-amino-2-(4-methoxybenzyl)-1*H*-imidazo[4,5-c]quinolin-1-yl]butyl}urea as an off white solid, m.p. 196 °C (decomposition). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.96 (d, J=7.9 Hz, 1H), 7.61 (d, J=8.3 Hz, 1H), 7.43 (t, J=7.6 Hz, 1H), 7.25 (m, 3H), 6.89 (d, J=8.6 Hz, 2H), 6.58 (broad s, 2H), 5.92 (broad s, 1H), 5.36 (broad s, 2H), 4.41 (m, 2H), 4.32 (s, 2H), 3.72 (s, 3H), 2.93 (d, J=5.8 Hz, 2H), 1.48 (m, 4H); MS (CI) m/e 419

Example 11

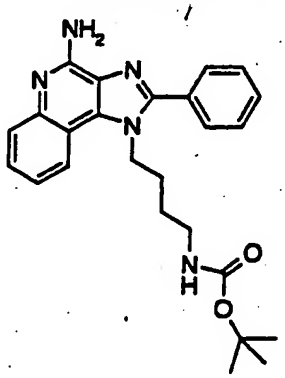
N^4-{4-[4-Amino-2-(2-methoxybenzyl)-1*H*-imidazo[4,5-c]quinolin-1-yl]butyl}-4-morpholinecarboxamide



According to the general method of Example 5, 1-(4-aminobutyl)-2-(4-methoxybenzyl)-1*H*-imidazo[4,5-c]quinolin-4-amine and 4-morpholinecarbonyl chloride were combined to provide N^4-{4-[4-amino-2-(2-methoxybenzyl)-1*H*-imidazo[4,5-c]quinolin-1-yl]butyl}-4-morpholinecarboxamide. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.81 (m, 2H), 7.50 (m, 1H), 7.30 (m, 2H), 7.17 (d, J=8.6 Hz, 2H), 6.86 (d, J=8.6 Hz, 2H), 5.62 (broad s, 2H), 4.36 (m, 2H), 4.31 (s, 2H), 3.78 (s, 3H), 3.64 (t, J=4.9 Hz, 4H), 3.25 (t, J=4.9 Hz, 4H), 3.18 (m, 2H), 1.70 (m, 2H), 1.54 (m, 2H); MS (EI) m/e 488.2533 (488.2536 calcd for $C_{27}H_{32}N_6O_3$).

Example 12

tert-Butyl N-[4-(4-Amino-2-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-l)butyl]carbamate



Part A

A solution of benzoyl chloride (5.3 g, 37.7 mmol) in dichloromethane (100 mL) was slowly added to a solution of *tert*-butyl N-{4-[(3-aminoquinolin-4-

yl)amino]butyl}carbamate (12.5 g, 37.7 mmol) in dichloromethane (250 mL) at ambient temperature. The reaction mixture was maintained at ambient temperature overnight. The resulting precipitate was isolated by filtration and dried to provide 11.0 g of *tert*-butyl N-(4-{[3-(benzoylamino)quinolin-4-yl]amino}butyl)carbamate hydrochloride as a white solid.

Part B

Triethylamine (7.26 g, 71.7 mmol) was added to a solution of the material from Part A in ethanol (200 mL) and heated at reflux for 2 days. The reaction mixture was concentrated to provide an orange syrup. HPLC mass spec analysis showed that the syrup contained the desired product and starting material. The syrup was taken up in dichloromethane (100 mL) and then cooled in an ice bath. Triethylamine (5 mL) and benzoyl chloride (1.9 mL) were added. The reaction mixture was maintained at ambient temperature for 2 days at which time analysis by HPLC indicated that the reaction was not complete. The reaction mixture was concentrated under vacuum. The residue was taken up in isopropyl alcohol (150 mL). Triethylamine (5 mL) was added and the reaction mixture was heated at reflux overnight. The reaction mixture was concentrated under vacuum. The residue was purified by flash chromatography (silica gel; eluting with 10% methanol in dichloromethane). The fractions containing product were combined and concentrated under vacuum. The residue was recrystallized from acetonitrile to provide 6.7 g of *tert*-butyl N-[4-(2-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]carbamate as a solid, m.p. 158-159°C.

Part C

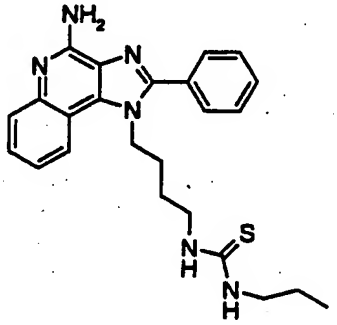
3-Chloroperoxybenzoic acid (1.05 eq of 65%) was slowly added in small portions to a solution of *tert*-butyl N-[4-(2-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]carbamate (6.56 g, 15.75 mmol) in dichloromethane (120 mL). After 3 hours the reaction was quenched with 1% aqueous sodium bicarbonate (200 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (2 X 50 mL). The organic fractions were combined, dried over magnesium sulfate and then concentrated under vacuum to provide a pale orange syrup. The syrup was triturated with diethyl ether to provide 6.8 g of 1-[4-(*tert*-butylcarbamyl)butyl]-2-phenyl-1*H*-imidazo[4,5-*c*]quinoline-5N-oxide as a pale tan solid, m.p. 178-181°C.

Part D

A solution of 1-[4-(*tert*-butylcarbamyl)butyl]-2-phenyl-1*H*-imidazo[4,5-*c*]quinoline-5N-oxide (6.8 g, 15.75 mmol) in dichloromethane (100 mL) was chilled in an ice bath. Concentrated ammonium hydroxide (30 mL) was added. Tosyl chloride (3.0 g, 15.75 mmol) was added in small portions over a period of 30 minutes. The reaction mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with water (350 mL). The layers were separated. The aqueous layer was extracted with dichloromethane. The organic fractions were combined, dried over magnesium sulfate and then concentrated under vacuum to provide a tan solid. This material was purified by flash chromatography (silica gel eluting with 10% methanol in dichloromethane) to provide 4.8 g of product. A small portion was recrystallized from toluene to provide *tert*-butyl N-[4-(4-amino-2-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]carbamate as a solid, m.p. 182-183°C. Analysis: Calculated for $C_{25}H_{29}N_5O_2$: %C, 69.58; %H, 6.77; %N, 16.22; Found: %C, 69.86; %H, 6.95; %N, 15.80.

Example 13

N-[4-(4-Amino-2-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-N'-propylthiourea



Part A

The *tert*-butyl N-[4-(4-amino-2-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]carbamate (4.3 g, 10.0 mmol) was dissolved in methanol (15 mL) and 1 N hydrochloric acid (100 mL) and then heated at reflux for 2 hours. The reaction mixture was concentrated under vacuum to a volume of about 50 mL. Addition of concentrated ammonium hydroxide to pH 12 did not produce a precipitate. The pH was adjusted to 7 with 1 N hydrochloric acid. The mixture was extracted with dichloromethane and then

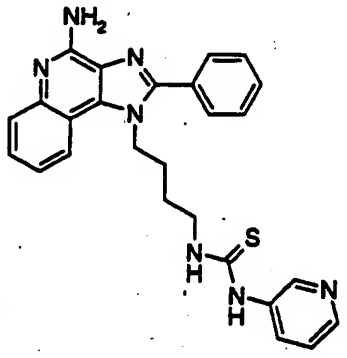
with ethyl acetate. The aqueous layer was concentrated to dryness. The residue was dissolved in water (50 mL) and then extracted continuously with refluxing chloroform for 36 hours. The chloroform extract was concentrated under vacuum to provide a light tan solid. This material was recrystallized from acetonitrile to provide 2.5 g of 1-(4-aminobutyl)-2-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as an off white solid, m.p. 175-177°C. Analysis: Calculated for $C_{20}H_{21}N_5$: %C, 72.48; %H, 6.39; %N, 21.13; Found: %C, 72.72; %H, 6.32; %N, 20.71.

Part B

A solution of propyl isothiocyanate (0.78 g, 7.72 mmol) in chloroform (5 mL) was added at ambient temperature to a solution of 1-(4-aminobutyl)-2-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.256 g, 7.72 mmol) in a mixture of chloroform (25 mL) and pyridine (5 mL). The reaction mixture was maintained at ambient temperature over the weekend. The reaction was quenched with ethanol and then concentrated under vacuum to provide a pale orange syrup. This material was purified by flash chromatography (silica gel, eluting with 10% methanol in dichloromethane). The pure fractions were combined and concentrated under vacuum to provide 0.22 g of N-[4-(4-amino-2-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-N'-propylthiourea as a white solid, m.p. 113-116°C. Mass spec M+1=433.2.

Example 14

N-[4-(4-Amino-2-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-N'-(3-pyridyl)thiourea

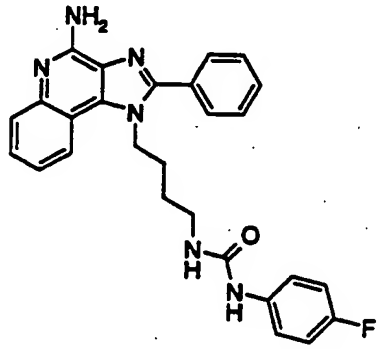


A solution of pyridine-3-isothiocyanate (0.136 g, 1.0 mmol) in chloroform (5 mL) was added at ambient temperature to a solution of 1-(4-aminobutyl)-2-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.331 g, 1.0 mmol) in a mixture of chloroform (25 mL)

and pyridine (5 mL). The reaction mixture was maintained at ambient temperature over the weekend. The reaction was quenched with ethanol and then concentrated under vacuum to provide an off-white solid. This material was purified by flash chromatography (silica gel, eluting with 10% methanol in dichloromethane). The pure fractions were combined and concentrated under vacuum to provide 0.2 g of N-[4-(4-amino-2-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-N'-(3-pyridyl)thiourea as a white solid, m.p. 118-120°C. Mass spec M+1=468.3. Analysis: Calculated for $C_{26}H_{25}N_7S$: %C, 66.79; %H, 5.39; %N, 20.97; Found: %C, 64.29; %H, 5.46; %N, 20.06.

Example 15

N-[4-(4-amino-2-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-N'-(4-fluorophenyl)urea

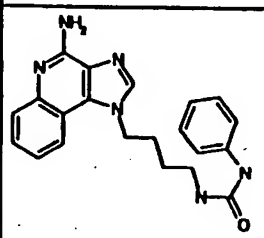
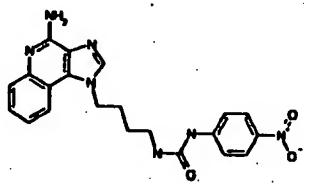


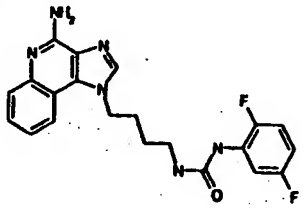
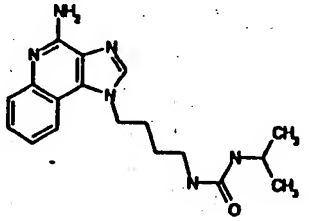
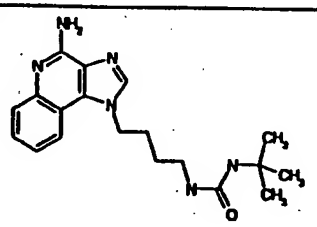
A solution of 4-fluorophenylisocyanate (0.137 g, 1.0 mmol) in chloroform (5 mL) was added at ambient temperature to a solution of 1-(4-aminobutyl)-2-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.331 g, 1.0 mmol) in a mixture of chloroform (25 mL) and pyridine (5 mL). The reaction mixture was maintained at ambient temperature over the weekend. The reaction was quenched with ethanol. The resulting pale yellow precipitate (identified as the bis-adduct) was isolated by filtration. The filtrate was concentrated under vacuum to provide an off-white solid. This material was purified by flash chromatography (silica gel, eluting with 10% methanol in dichloromethane). The pure fractions were combined and concentrated under vacuum to provide 0.22 g of N-[4-(4-amino-2-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-N'-(4-fluorophenyl)urea as a white solid, m.p. 145-150°C. Mass spec M+1=469.2. Analysis: $C_{27}H_{25}FN_6O$: %C, 69.21; %H, 5.37; %N, 17.94; Found: %C, 66.70; %H, 5.33; %N, 17.03.

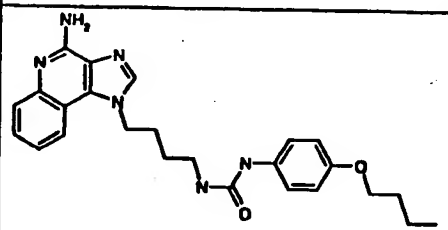
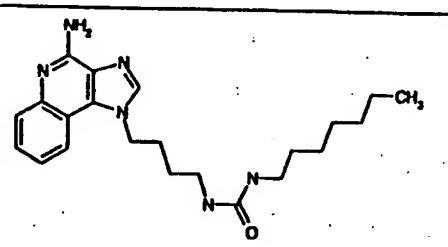
Examples 16 - 52

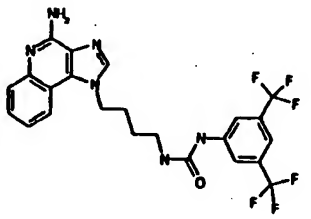
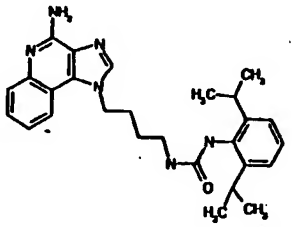
The compounds shown in the table below were made according to the synthetic method of Reaction Scheme II above.

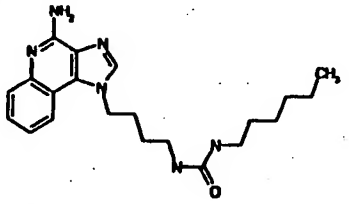
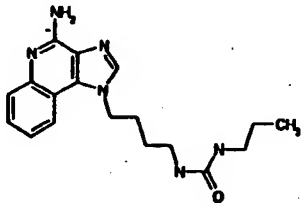
A solution of 1-(4-aminobutyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (36 µmol) in 10 mL of dichloromethane in a screw-capped test tube was cooled down to -5°C. The isocyanate (45 µmol) was added as a 0.3 M solution in dichloromethane. Argon was bubbled through the mixture during addition and for an additional 15 seconds, and the mixture was allowed to stand at -5°C overnight. To this mixture was added approximately 90 mg of an aminomethyl polystyrene resin (0.62 meq/g, 100-200 mesh), and the mixture was warmed to reflux and shaken at about 600 rpm for 3 hours. The mixtures were filtered through Poly-Prep columns (Bio-Rad #731-1550) to remove resin. Three different purification methods were used. In Method A the filtrate was loaded onto a silica gel column. The column was eluted with 10:1 dichloromethane:methanol and the fractions containing product were combined and dried in vacuo. In Method C the filtrates were dried in vacuo and purified by semi-preparative hplc on a Gilson system (Rainin Microsorb C18 column , 21.4 x 250 mm, 8 micron particle size, 60A pore, 10 mL/min., gradient elution from 2-95% B in 25 min., hold at 95% B for 5 min., where A=0.1 % trifluoroacetic acid/water and B=0.1% Trifluoroacetic acid/acetonitrile, peak detection at 254 nm for triggering fraction collection). The semi-prep hplc fractions were analyzed by LC-APCI/MS and the appropriate fractions were lyophilized to provide the compounds as trifluoroacetate salts. In Method B the compounds were purified by Method C and then the trifluoroacetate salts were dissolved in ca. 3-5 mL of 2:1 dichloromethane-methanol and shaken with ca. 80 mg (300 µmol) of diisopropylaminomethyl-polystyrene resin (Argonaut PS-DIEA, 3.86 mmol/g) for 1-2 h to liberate the free amine, and then filtered and dried in vacuo. The compounds were generally amorphous solids.

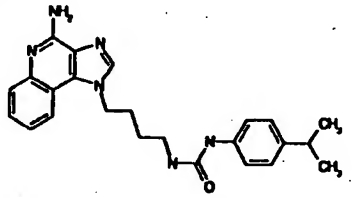
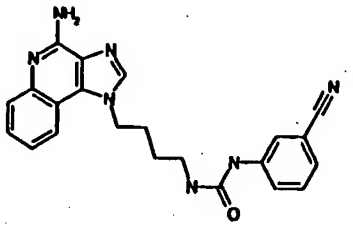
Example No.	Structure	Purification	APCI-MS m/e	500 MHz ^{1}H NMR
16		A	375.19	(DMSO-d_6) δ 8.38 (s,1H), 8.22 (s,1H), 8.05 (d,J=7.9Hz,1H), 7.61 (d,7.9Hz,1H), 7.43 (t,J=7.6Hz,1H), 7.36 (d,J=7.3Hz,2H), 7.24 (t,J=7.3Hz,1H), 7.20 (t,J=7.9Hz,2H), 6.87 (t,J=7.3Hz,1H), 6.60 (bs,2H), 6.14 (t,J=5.8Hz,1H), 4.63 (t,J=7Hz,2H), 3.15 (q,J=6Hz,2H), 1.88 (quintet,J=7Hz,2H), 1.49 (quintet,J=7Hz,2H)
17		B	420.16	(DMSO-d_6) δ 9.37 (s,1H), 8.42 (s,1H), 8.16 (d,J=7.8Hz,1H), 8.12 (d,J=9.3Hz,2H), 7.74 (d,J=8.3Hz,1H), 7.59 (m,3H), 7.43 (t,J=6Hz,1H), 6.58 (t,J=5.4Hz,1H), 4.68 (t,J=7Hz,2H), 3.15 (q,J=6Hz,2H), 1.89 (quintet,J=7.5Hz;2H), 1.52 (quintet,J=7Hz,2H)

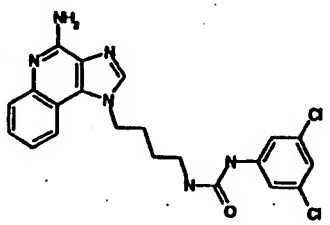
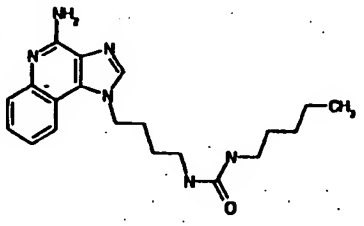
Example No.	Structure	Purification	APCI-MS m/e	500 MHz ^{1}H NMR
18		C	411.17	
19		B	341.22	(DMSO-d_6) δ 8.40 (s,1H), 8.15 (d,J=7.8Hz,1H), 7.75 (d,J=8.1Hz,1H), 7.62 (t,J=7Hz,1H), 7.46 (s,J=7Hz,1H), 5.71 (t,J=7Hz,1H), 5.60 (d,J=8Hz,1H), 4.65 (t,J=6.5Hz,2H), 3.61 (sextet,J=7.5Hz,1H), 3.01 (q,J=6Hz,2H), 1.84 (quintet,J=7.5Hz,2H), 1.42 (quintet,J=7Hz,2H), 0.97 (d,J=6.5Hz,6H)
20		B	355.24	(DMSO-d_6) δ 8.42 (s,1H), 8.17 (d,J=8.3Hz,1H), 7.76 (d,J=8.3Hz,1H), 7.64 (t,J=8.5Hz,1H), 7.48 (s,1H), 5.66 (t,J=6Hz,1H), 5.54 (s,1H), 4.66 (t,J=7Hz,2H), 2.98 (q,J=6Hz,2H), 1.84 (quintet,J=8Hz,2H), 1.41 (quintet,J=8Hz,2H), 1.17 (s,9H)

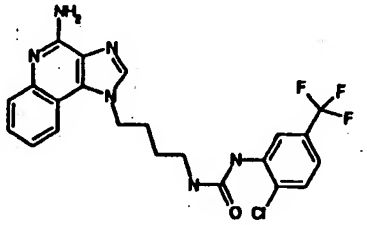
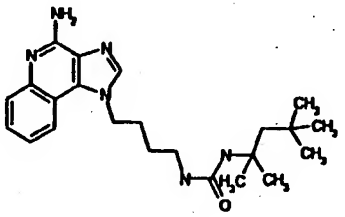
Example No.	Structure	Purification	APCI-MS m/e	500 MHz ^{1}H NMR
21		B	447.21	(DMSO-d_6) δ 8.43 (s,1H), 8.3 (br s,1H), 8.26 (s,1H), 8.17 (d,J=7.8Hz,1H), 7.75 (d,J=8.3Hz,1H), 7.61 (t,J=8.1Hz,1H), 7.44 (t,J=7.8Hz,1H), 7.23 (d,J=6.8Hz,2H), 6.78 (d,J=6.8Hz,2H), 6.12 (t,J=6.1Hz,1H), 4.68 (t,J=7Hz,2H), 3.88 (t,J=6.5Hz,2H), 3.11 (q,J=6Hz,2H), 1.88 (quintet,J=7Hz,2H), 1.66 (quintet,J=8Hz,2H), 1.49 (quintet,J=7Hz,2H), 1.41 (quintet,J=7Hz,2H), 0.92 (t,J=7Hz,3H)
22		B	447.00	(DMSO-d_6) δ 8.39 (s, 1H), 8.28 (bs,1H), 8.15 (d,J=7.8Hz,1H), 7.75 (d,J=7.8Hz,1H), 7.61 (t,J=7.8Hz,1H), 7.45 (t,J=7.6Hz,1H), 5.81 (t,J=6Hz,1H), 5.75 (t,J=6Hz,1H), 4.65 (t,J=7.5Hz,2H), 3.02 (q,J=6.5Hz,2H), 2.92 (q,J=6.0Hz,2H), 1.84 (quintet,J=7.5Hz,2H), 1.43 (quintet,J=7Hz,2H), 1.30 (quintet,J=7Hz,2H), 1.22 (bs,J=8Hz,8H), 0.84 (t,J=7.5Hz,3H)

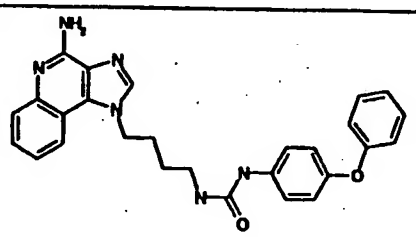
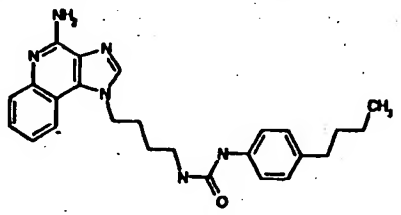
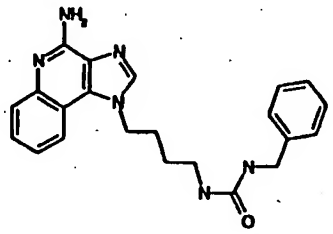
Example No.	Structure	Purification	APCI-MS m/e	500 MHz ^{1}H NMR
23		B	511.11	(DMSO-d_6) δ 9.6-8.6 (b,2H), 9.35 (s,1H), 8.55 (s,1H), 8.24 (d,J=8.0Hz,1H), 8.06 (s,2H), 7.82 (d,J=8.0Hz,1H), 7.69 (t,J= 8.0Hz,1H), 7.55 (t,J= 8.0Hz,1H), 7.54 (s,1H), 6.70 (t,J=6.0,1H), 4.72 (t,J=7.5 Hz,2H), 3.15 (q,J=6.0Hz,2H), 1.90 (quintet,J=7.0 Hz,2H), 1.54 (quintet,J=7.5 Hz,2H)
24		B	459.35	(DMSO-d_6) δ 8.32 (bs,1H), 8.28 (bs,1H), 8.13 (d,J=8.8Hz,1H), 7.70 (d,J=7.6Hz,1H), 7.55 (t,J=6.8Hz,1H), 7.38 (t,1H), 7.34 (bs,1H), 7.17 (t,J=8Hz,1H), 7.06 (d,J=8Hz,2H), 6.1 (bs,2H), 4.66 (t,J=7.5Hz,2H), 3.10 (bs,2H), 3.04 (quintet,J=7Hz,1H), 1.88 (bm,2H), 1.48 (bm,2H), 1.02 (d,J=7Hz,12H)

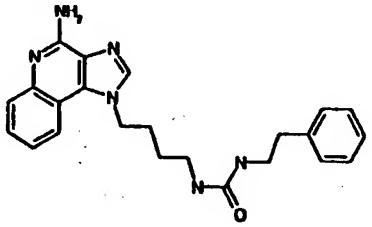
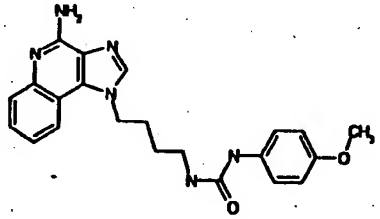
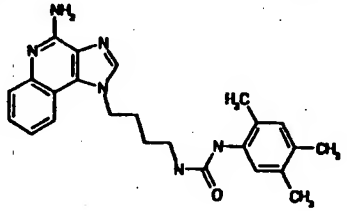
Example No.	Structure	Purification	APCI-MS m/e	500 MHz ^{1}H NMR
25		C	383.22	(DMSO-d_6) δ 8.52 (s,1H), 8.22 (d,J=8Hz,1H), 7.83 (d,J=8Hz,1H), 7.72 (t,J=8Hz,1H), 7.58 (t,J=8Hz,1H), 5.80 (t,J=5Hz,1H), 5.75 (t,J=5.5Hz,1H), 4.68 (t,J=7.0Hz,2H), 3.02 (q,J=6.5Hz,2H), 2.92 (q,J=6Hz,2H), 1.84 (quintet,J=7Hz,2H), 1.44 (quintet,J=7Hz,2H), 1.29 (t,J=7Hz,2H), 1.2 (m,6H), 0.84 (t,J=7Hz,3H)
26		C	341.21	(DMSO-d_6) δ 8.52 (s,1H), 8.23 (d,J=8Hz,1H), 7.83 (d,J=8Hz,1H), 7.72 (t,J=7.5Hz,1H), 7.57 (t,J=7Hz,1H), 5.80 (t,J=6.5Hz,1H), 5.77 (t,J=6Hz,1H), 4.68 (t,J=7.5Hz,2H), 3.02 (q,J=6.5Hz,2H), 2.89 (q,J=6.5Hz,2H), 1.84 (quintet,J=7.5Hz,2H), 1.43 (quintet,J=8Hz,2H), 1.31 (sextet,J=7Hz,2H), 0.78 (t,J=7.5Hz,3H)

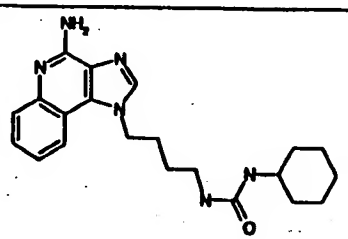
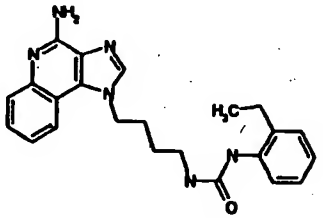
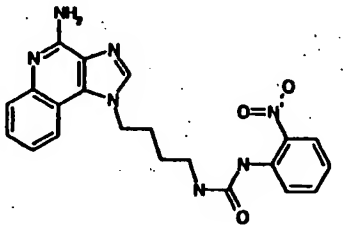
Example No.	Structure	Purification	APCI-MS m/e	500 MHz ^{1}H NMR
27		C	417.18	(DMSO-d_6) δ 9.6-8.6 (b,2H), 8.55 (s,1H), 8.33 (bs,1H), 8.24 (d,J=7.5Hz,1H), 7.83 (d,J=7.5Hz,1H), 7.72 (t,J=7.5 Hz,1H), 7.56 (t,J=7.5Hz,1H), 7.25 (d,J= 8.0Hz,2H), 7.06 (d,J=8 Hz,2H), 6.17 (t,J=5.5 Hz,1H), 4.71 (t,J=7.0 Hz,2H), 3.12 (q,J= 5.5 Hz,2H), 2.79 (quintet,J= 7.0 Hz,1H), 1.89 (quintet,J= 7.0Hz,2H), 1.51 (quintet,J=7.0 Hz,2H), 1.16 (d,J= 7.0Hz,6H)
28		B	400.18	(DMSO-d_6) δ 8.88 (s,1H), 8.32 (s,1H), 8.22 (bs,1H), 8.11 (d,J=8Hz,1H), 7.91 (t,J=1.7Hz,1H), 7.68 (d,J=8Hz,1H), 7.55 (d,J=9.5Hz,1H), 7.51 (t,J=8.1Hz,1H), 7.41 (t,J=8.3Hz,1H), 7.34 (t,J=7.1Hz,1H), 6.41 (t,J=7Hz,1H), 4.66 (t,J=6.5Hz,2H), 3.13 (q,J=6Hz,2H), 1.89 (quintet,J=7.5Hz,2H), 1.50 (quintet,J=7Hz,2H)

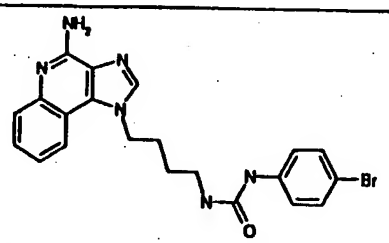
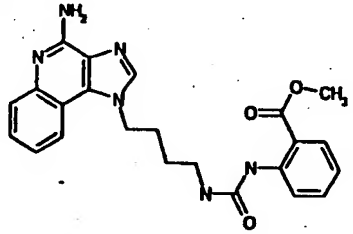
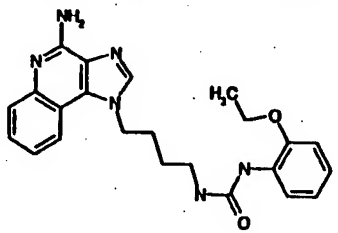
Example No.	Structure	Purification	APCI-MS m/e	500 MHz ^{1}H NMR
29		B	443.10	(DMSO-d_6) δ 8.97 (s,1H), 8.46 (s,1H), 8.19 (d,J=7.8Hz,1H), 7.77 (d,J=8.3Hz,1H), 7.63 (t,J=8.1Hz,1H), 7.48 (t,J=7.3Hz,1H), 7.44 (s,2H), 7.05 (t,J=1.7Hz,1H), 6.49 (t,J=5.6Hz,1H), 4.69 (t,J=7Hz,2H), 3.12 (q,J=6.5Hz,2H), 1.88 (quintet,J=8Hz,2H), 1.50 (quintet,J=7Hz,2H)
30		B	369.24	(DMSO-d_6) δ 8.80 (b, 2H), 8.52 (s, 1H), 8.23 (d, J= 7.5 Hz, 1H), 7.84 (d,J=8.0Hz,1H), 7.73 (t,J=8.0Hz,1H), 7.58 (t J=7.5Hz,1H), 5.80 (t, J=5.5Hz,1H), 5.75 (t, J=5.5Hz,1H), 4.68 (t, J= 7.0Hz,2H), 3.02 (q, J=5.5Hz,2H), 2.92 (q, J=5.5Hz,2H), 1.84 (quintet,J= 7.0Hz,2H), 1.44 (quintet, J= 7.0 Hz,2H), 1.30 (quintet, J= 7.0Hz,2H), 1.23 (quintet, J=7.0 Hz,2H), 1.18 (sextet, J= 7.0Hz,2H), 0.83 (t,J=7.0Hz,3H)

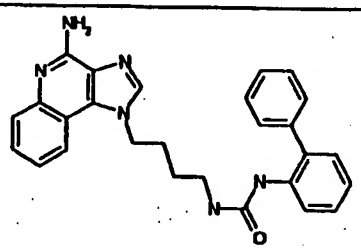
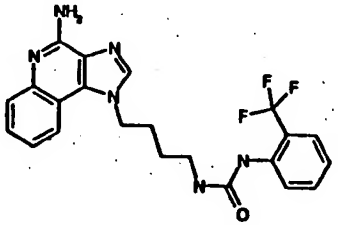
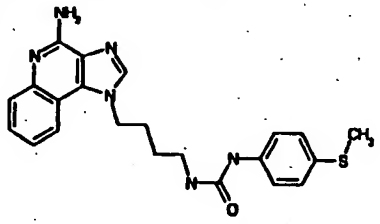
Example No.	Structure	Purification	APCI-MS m/e	500 MHz ^{1}H NMR
31		B	477.08	(DMSO-d_6) δ 9.6-8.6 (b, 2H), 8.60 (d, J= 2.0 Hz, 1H), 8.56 (s, 1H), 8.26 (s, 1H), 8.25 (d, J=8 Hz, 1H), 7.82 (d, J=8.0 Hz, 1H), 7.69 (t, j=8.0 Hz, 1H), 7.64 (d, J= 8.0 Hz, 1H), 7.55 (t, J=8.0 Hz, 1H), 7.28 (dd, J=8.0, 2.0 Hz, 1H), 7.23 (t, J=5.5 Hz, 1H), 4.72 (t, J= 7.0 Hz, 2H), 3.16 (q, J= 5.5 Hz, 2H), 1.92 (quintet, J= 7Hz, 2H), 1.54 (quintet, J= 7.0 Hz, 2H)
32		B	411.23	(DMSO-d_6) δ 9.6-8.6 (b,2H), 8.53 (s,1H), 8.24 (d,J=8.5Hz,1H), 7.84 (d,J=8.5Hz,1H), 7.74 (t,J=8.5Hz,1H), 7.59 (t,J=8.5 Hz,1H), 5.63 (t,J=6.0Hz,1H), 5.44 (s,1H), 4.70 (t,J=7.0Hz,2H), 2.98 (q,J=6.0Hz,2H), 1.83 (quintet,J=7.0Hz,2H), 1.59 (s,2H), 1.40 (quintet, J=7.0Hz,2H), 1.19 (s,6H), 0.84 (s,9H)

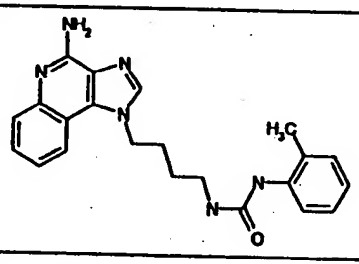
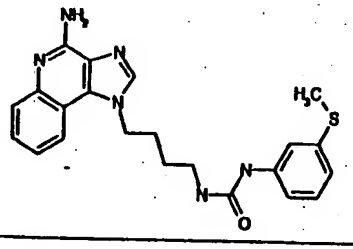
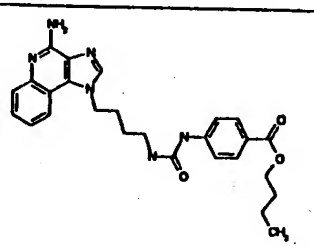
Example No.	Structure	Purification	APCI-MS m/e	500 MHz ^{1}H NMR
33		C	467.21	
34		C	431.26	
35		C	389.20	

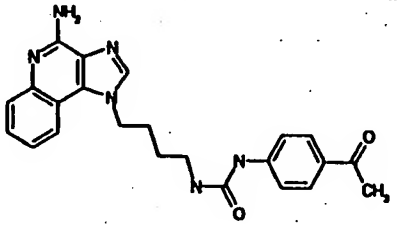
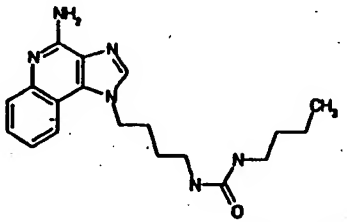
Example No.	Structure	Purification	APCI-MS m/e	500 MHz ^{1}H NMR
36		C	403.22	
37		C	405.19	
38		C	417.24	

Example No.	Structure	Purification	APCI-MS m/e	500 MHz ^{1}H NMR
39		C	381.26	
40		C	403.23	
41		C	420.18	

Example No.	Structure	Purification	APCI-MS m/e	500 MHz ^{1}H NMR
42		C	453.09	
43		C	433.18	
44		C	419.18	

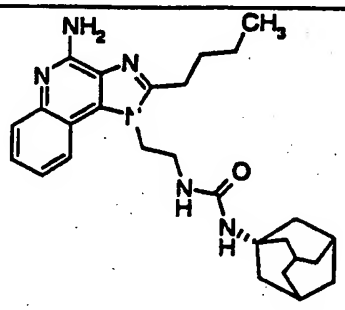
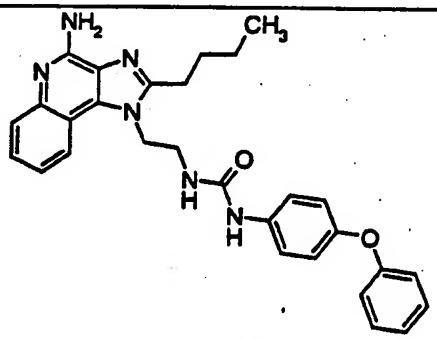
Example No.	Structure	Purification	APCI-MS m/e	500 MHz ^{1}H NMR
45		C	451.17	
46		C	443.14	
47		C	421.14	

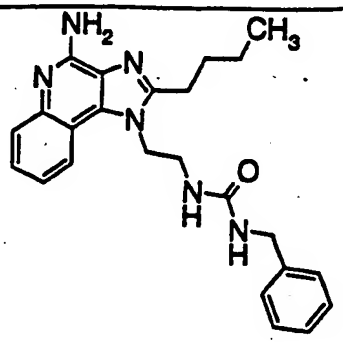
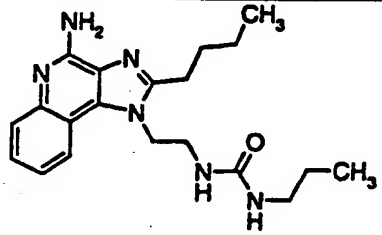
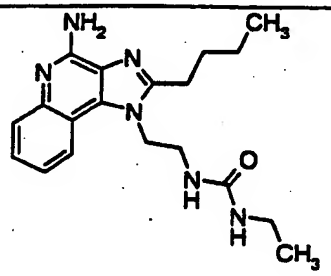
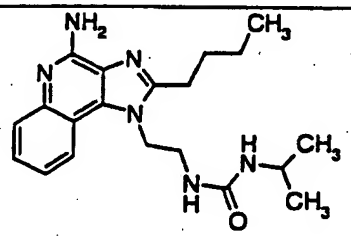
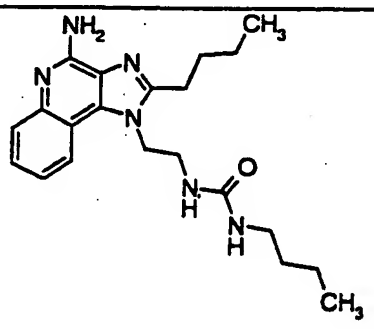
Example No.	Structure	Purification	APCI-MS m/e	500 MHz ^{1}H NMR
48		C	389.18	
49		C	421.14	
50		C	475.20	

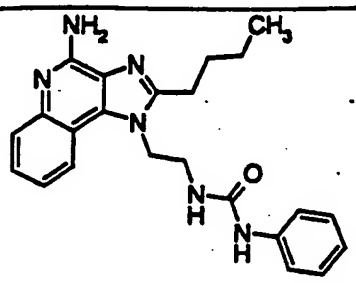
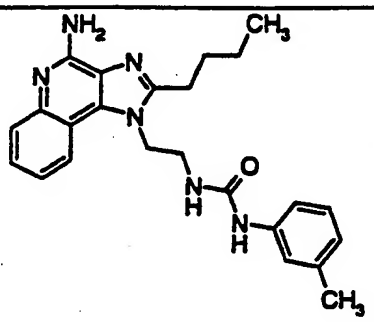
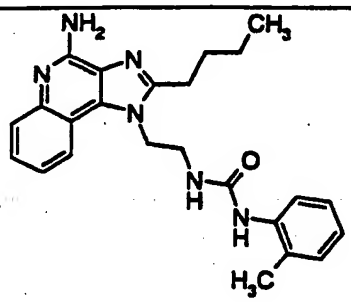
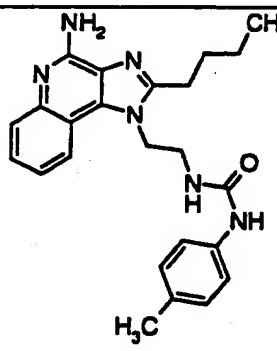
Example No.	Structure	Purification	APCI-MS m/e	500 MHz ^{1}H NMR
51		C	417.20	
52		C	355.21	

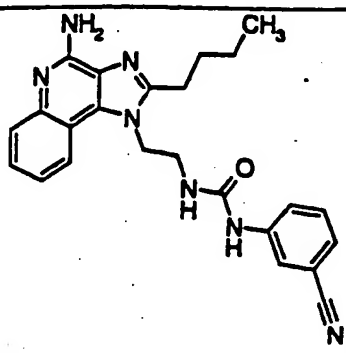
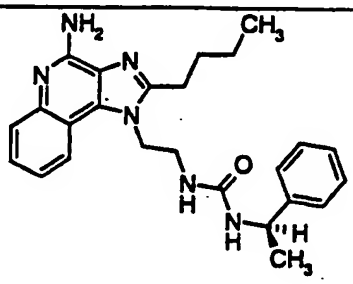
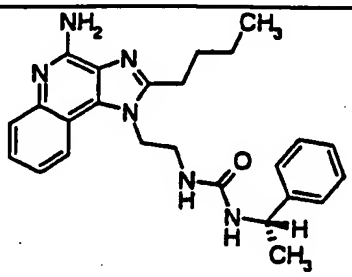
Examples 53 - 66

The examples in the table below were prepared according to the synthetic method of Reaction Scheme II above using the following general method. 1-(2-Aminoethyl)-2-butyl-1*H*-imidazo[4,5-c]quinolin-4-amine (50 mg), dichloromethane (2 mL) and the isocyanate were placed in a 2 dram (7.4 mL) vial. The vial was placed on a shaker for about 2 – 16 hours at ambient temperature. The reaction mixture was analyzed by LC/MS to confirm the formation of the desired product. The solvent was removed and the residue was purified by semi-preparative HPLC (Capcell Pak C18 column, 35 mm x 20 mm, 5 micron particle size, 20 mL/min., gradient elution from 5-95% B in 10 min., hold at 95% B for 2 min., where A=0.1 % trifluoroacetic acid/water and B=0.1 % trifluoroacetic acid/acetonitrile, peak detection at 254 nm for triggering fraction collection). The semi-prep HPLC fractions were analyzed by LC-APCI/MS and the appropriate fractions were combined and lyophilized to provide the trifluoroacetate salt of the desired urea.

Example #	Structure of the Free Base	mass
53		461.2
54		495.1

Example #	Structure of the Free Base	mass
55		417.1
56		369.2
57		355
58		369.2
59		383.3

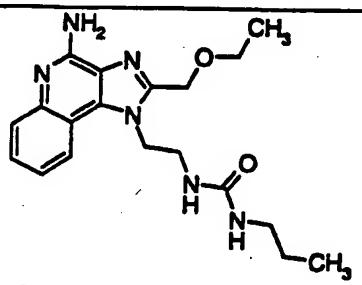
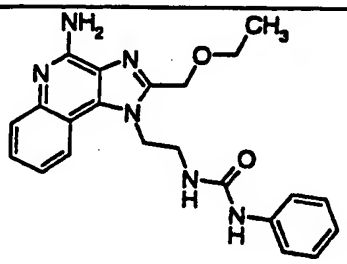
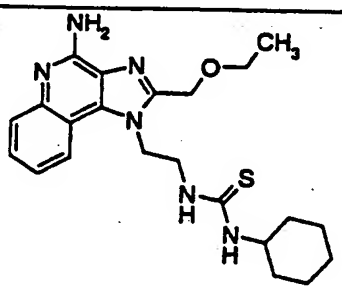
Example #	Structure of the Free Base	mass
60		403.2
61		417.2
62		417.2
63		417.2

Example #	Structure of the Free Base	mass
64		428.2
65		431.2
66		431.2

Examples 67 - 69

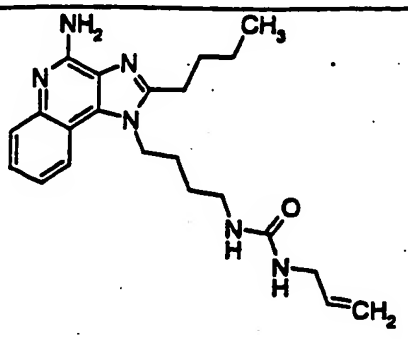
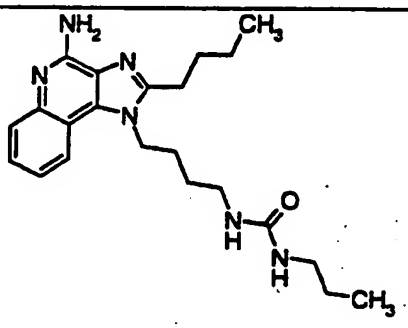
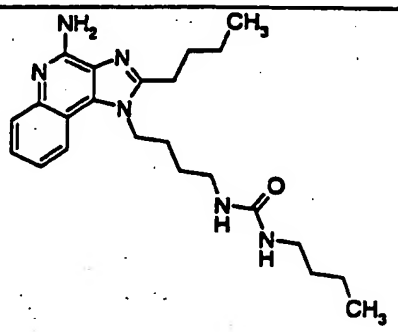
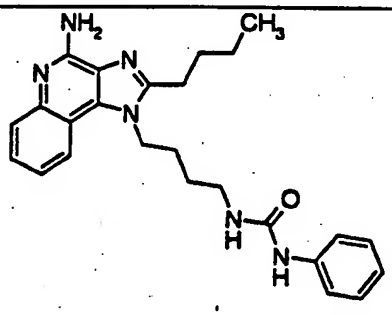
The examples in the table below were prepared using the following method. 1-(2-Aminoethyl)-2-ethoxymethyl-1*H*-imidazo[4,5-c]quinolin-4-amine hydrochloride (50 mg), dichloromethane (2 mL) and diisopropylethylamine (1.2 eq) were placed in a 2 dram (7.4 mL) vial. The vial was placed on a shaker for about 1 hour at ambient temperature. The appropriate (thio)isocyanate was added and the vial was shaken at ambient temperature for about 4 hours. The reaction mixture was analyzed by LC/MS to confirm the formation of the desired product. The solvent was removed and the residue was purified by semi-preparative HPLC (Capcell Pak C18 column, 35 mm x 20 mm, 5 micron particle size, 20 mL/min., gradient elution from 5-95% B in 10 min., hold at 95% B for 2 min., where A=0.1 % trifluoroacetic acid/water and B=0.1 % trifluoroacetic acid/acetonitrile, peak

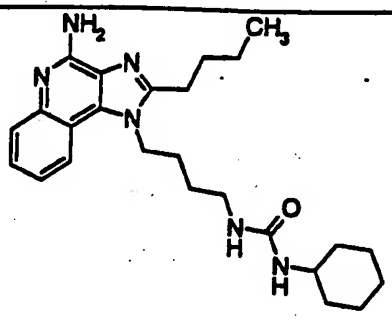
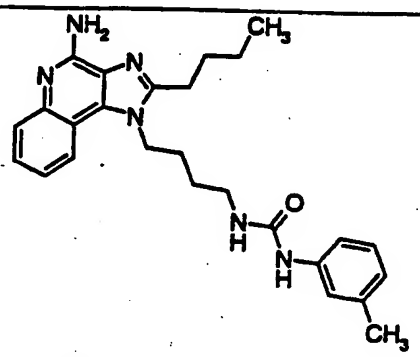
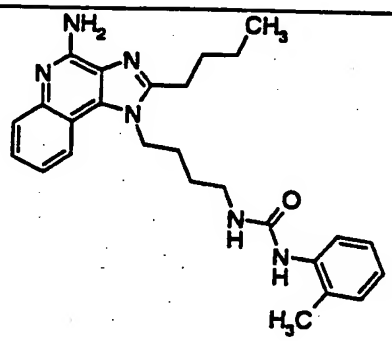
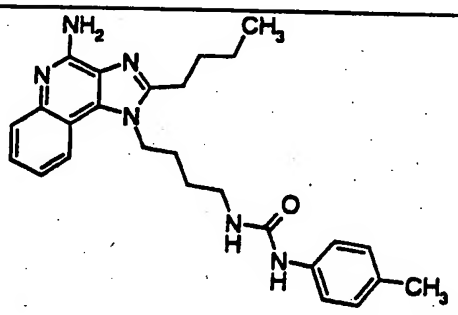
detection at 254 nm for triggering fraction collection). The semi-prep HPLC fractions were analyzed by LC-APCI/MS and the appropriate fractions were combined and lyophilized to provide the trifluoroacetate salt of the desired (thio)urea.

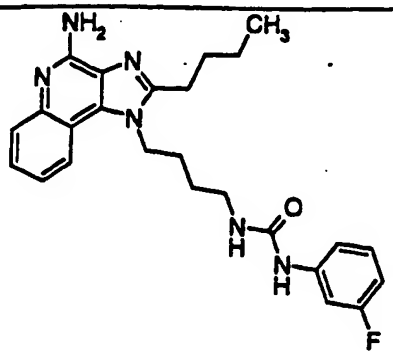
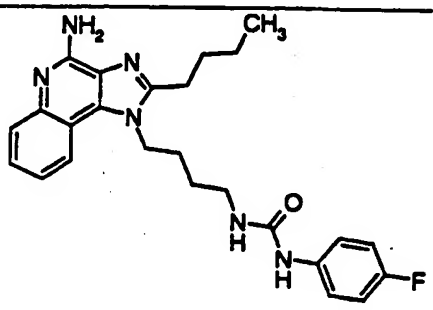
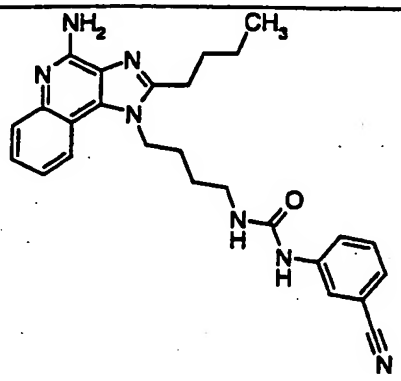
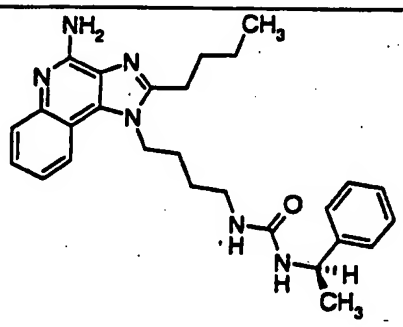
Example #	Structure of the Free Base	Mass
67		371.1
68		405.1
69		427.1

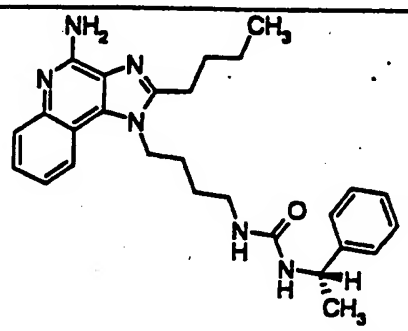
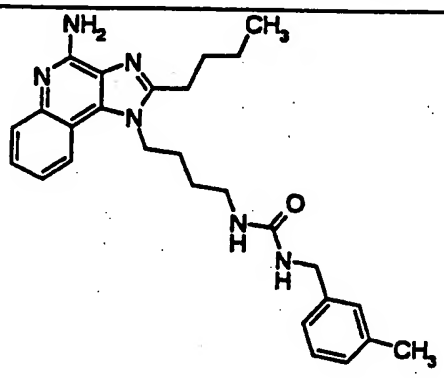
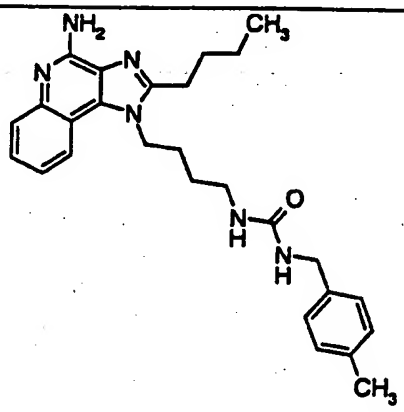
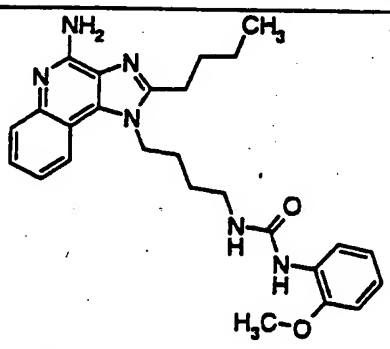
Examples 70 - 99

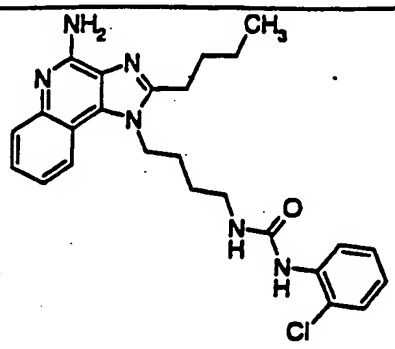
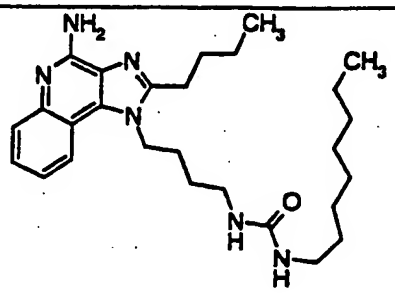
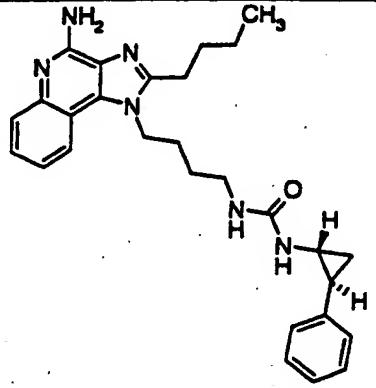
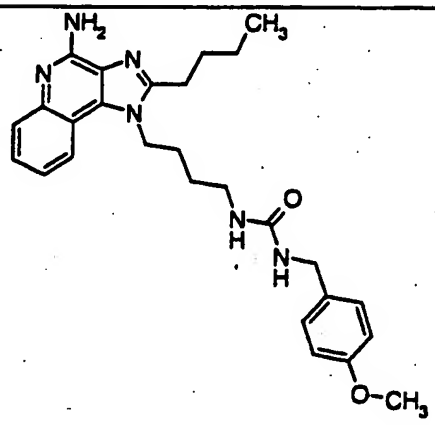
The examples in the table below were prepare according to the synthetic method of Reaction Scheme II above by reacting 1-(4-aminobutyl)-2-butyl-1*H*imidazo[4,5-*c*]quinolin-4-amine with the appropriate isocyanate using the general method of Examples 53 – 66 above.

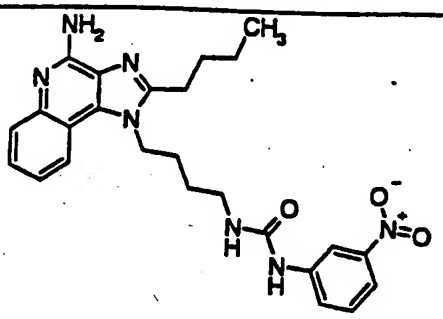
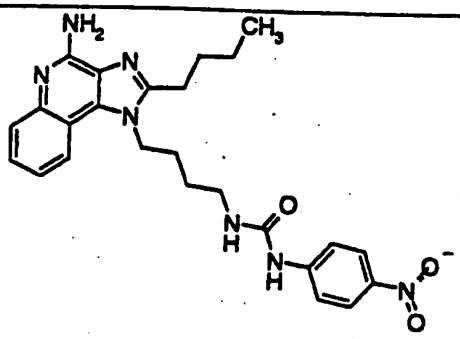
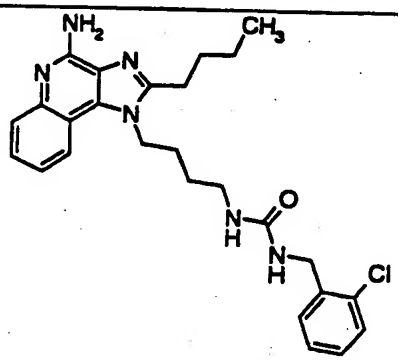
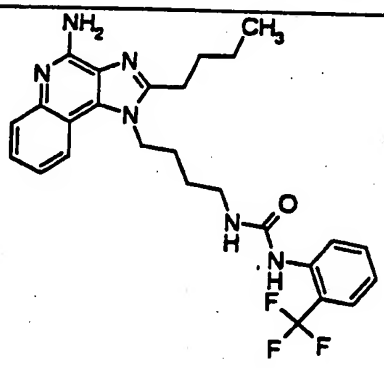
Example #	Structure of Free Base	Mass
70		395.2
71		397.3
72		411.3
73		431.2

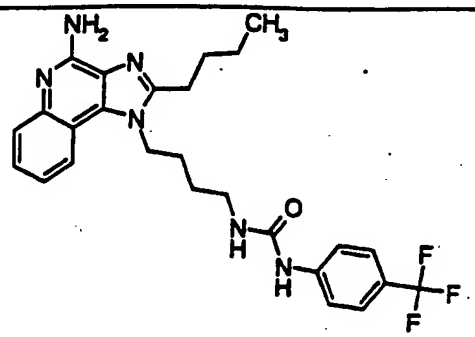
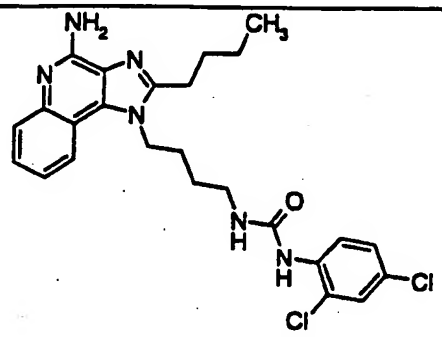
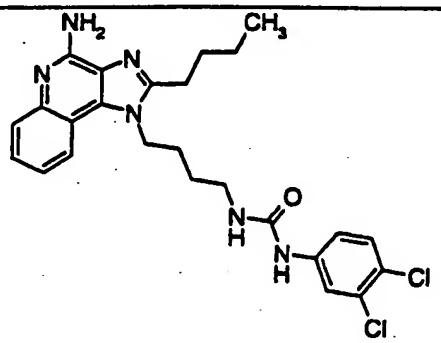
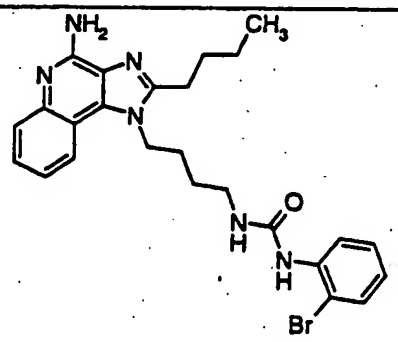
Example #	Structure of Free Base	Mass
74		437.3
75		445.2
76		445.20
77		445.2

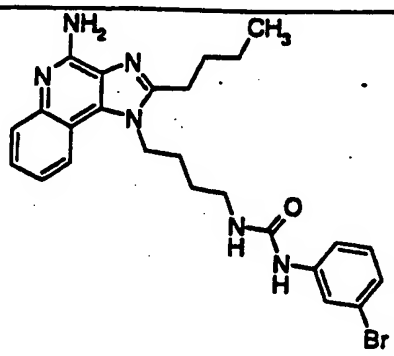
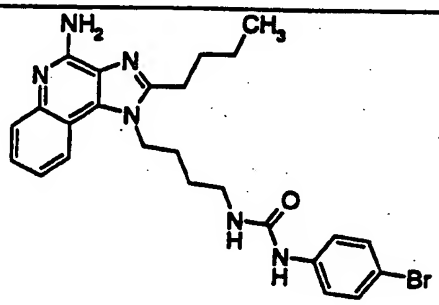
Example #	Structure of Free Base	Mass
78		449.2
79		449.2
80		456.2
81		459.3

Example #	Structure of Free Base	Mass
82		459.3
83		459.3
84		459.3
85		461.3

Example #	Structure of Free Base	Mass
86		465.2
87		467.3
88		471.3
89		475.3

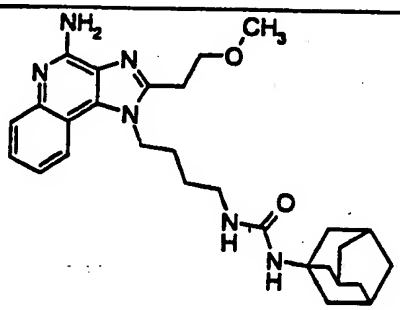
Example #	Structure of Free Base	Mass
90		476.2
91		476.2
92		479.2
93		499.2

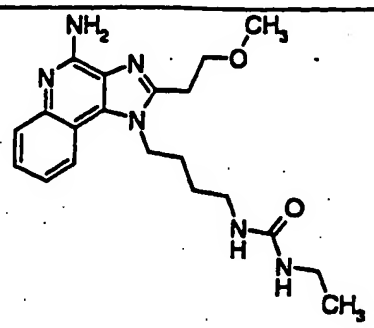
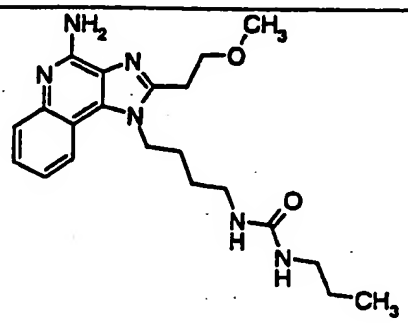
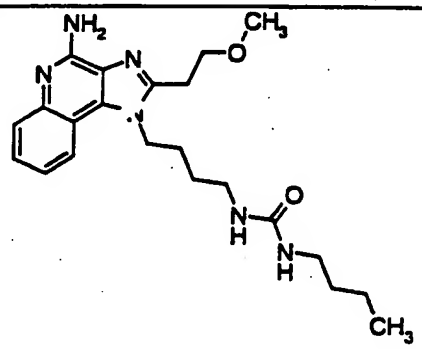
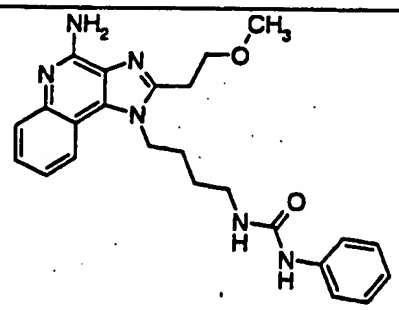
Example #	Structure of Free Base	Mass
94		499.2
95		499.2, 501.1
96		499.2, 501.1
97		509, 511.1

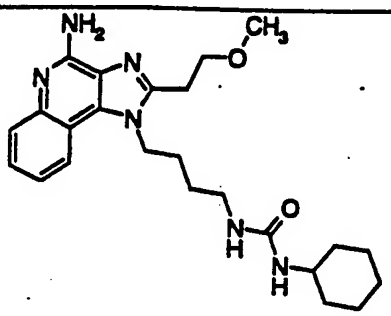
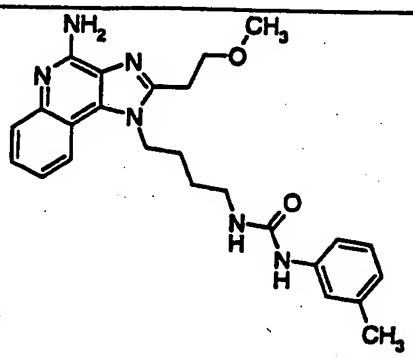
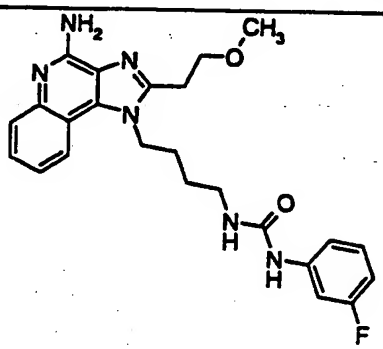
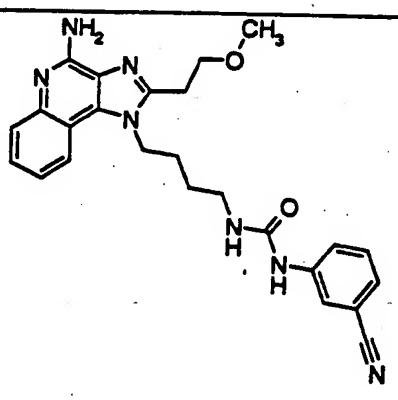
Example #	Structure of Free Base	Mass
98		509, 511.1
99		509, 511.1

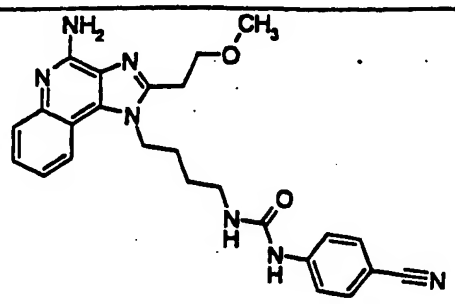
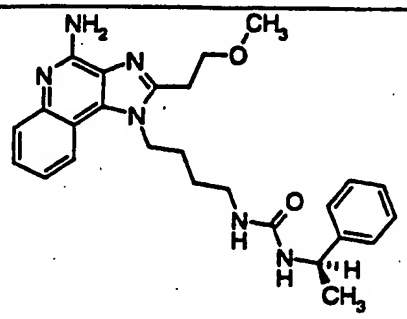
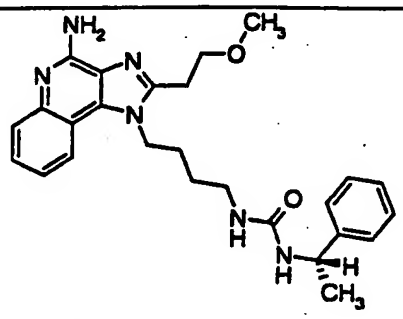
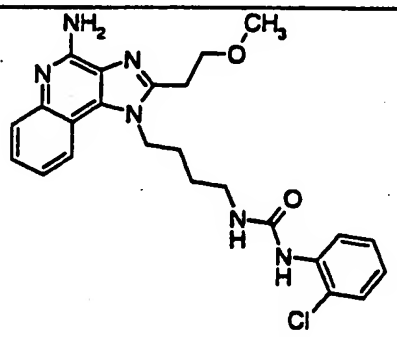
Examples 100 - 119

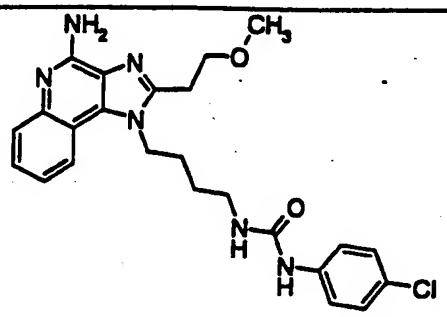
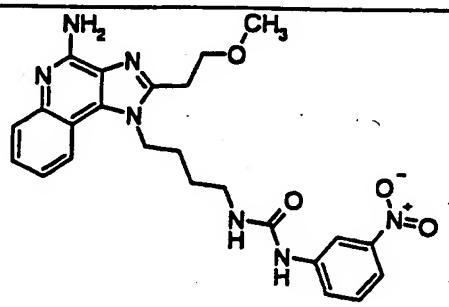
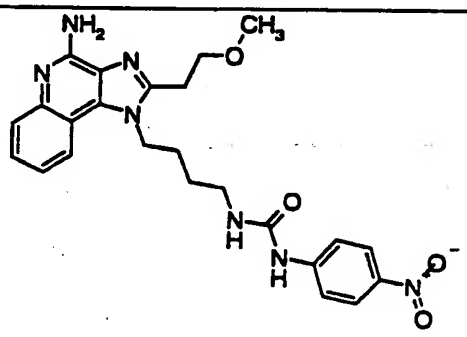
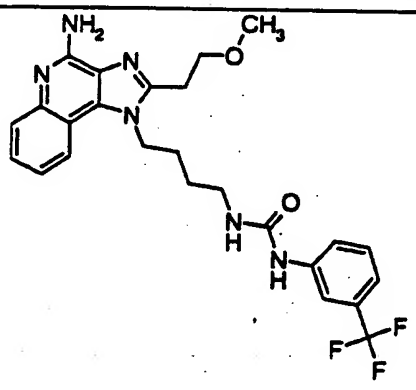
The examples in the table below were prepare according to the synthetic method of Reaction Scheme II above by reacting 1-(4-aminobutyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine with the appropriate isocyanate using the general method of Examples 53 - 66 above.

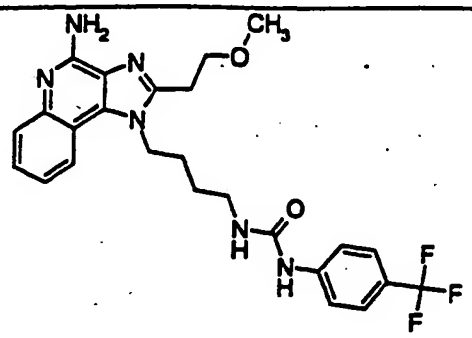
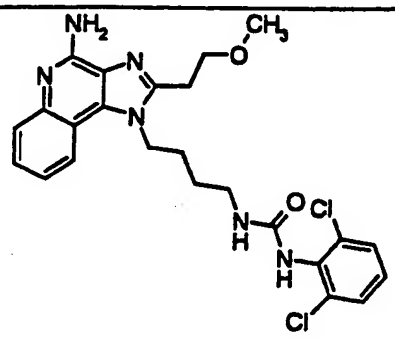
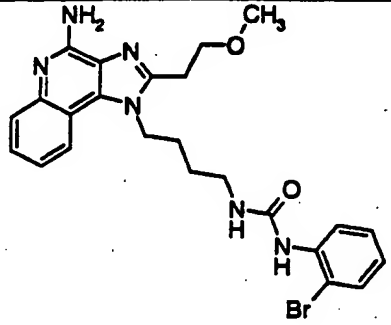
Example #	Structure of the Free Base	Mass
100		491.3

Example #	Structure of the Free Base	Mass
101		385.2
102		399.2
103		413.2
104		433.2

Example #	Structure of the Free Base	Mass
105		439.2
106		447.2
107		451.1
108		458.2

Example #	Structure of the Free Base	Mass
109		458.2
110		461.2
111		461.2
112		467.1

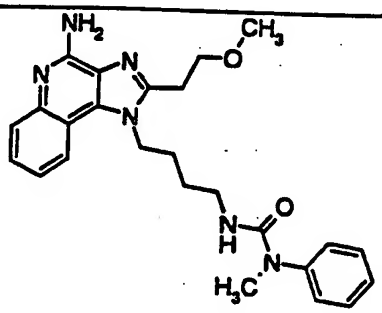
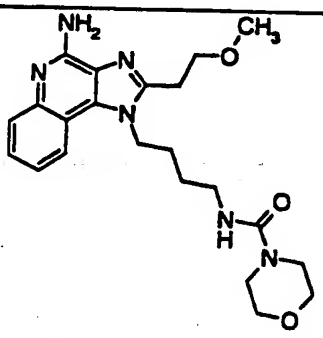
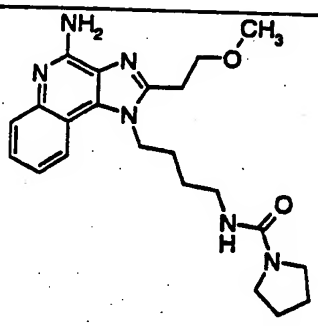
Example #	Structure of the Free Base	Mass
113		467.1
114		478.1
115		478.1
116		501.2

Example #	Structure of the Free Base	Mass
117		501.2
118		501.0, 503.1
119		511, 513.1

Examples 120 - 122

The examples in the table below were prepared according to the synthetic method of Reaction Scheme III above using the following method. 1-(4-Aminobutyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-c]quinolin-4-amine (50 mg), diisopropylethylamine (34 µL), dichloromethane (2 mL) and the carbamyl chloride (1.1 eq) were placed in a 2 dram (7.4 mL) vial. The vial was placed on a shaker for about 2 hours at ambient temperature. The reaction mixture was analyzed by LC/MS to confirm the formation of the desired product. The solvent was removed and the residue was purified by semi-preparative HPLC (Capcell Pak C18 column, 35 mm x 20 mm, 5 micron particle size, 20 mL/min., gradient

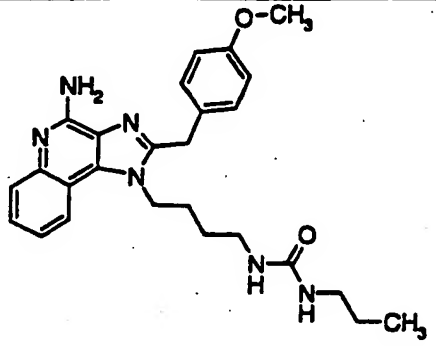
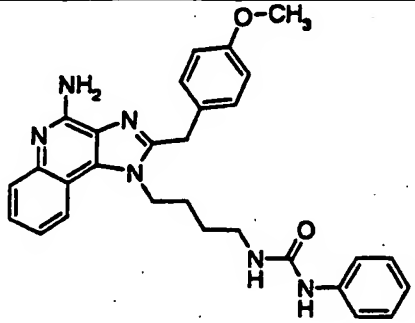
elution from 5-95% B in 10 min., hold at 95% B for 2 min., where A=0.1 % trifluoroacetic acid/water and B=0.1 % trifluoroacetic acid/acetonitrile, peak detection at 254 nm for triggering fraction collection). The semi-prep HPLC fractions were analyzed by LC-APCI/MS and the appropriate fractions were combined and lyophilized to provide the trifluoroacetate salt of the desired urea.

Example #	Structure of the Free Base	Mass
120		447.3
121		427.2
122		411.3

Examples 123 - 124

The examples in the table below were prepare according to the synthetic method of Reaction Scheme II above by reacting 1-(4-aminobutyl)-2-(4-methoxyphenylmethyl)-1*H*-

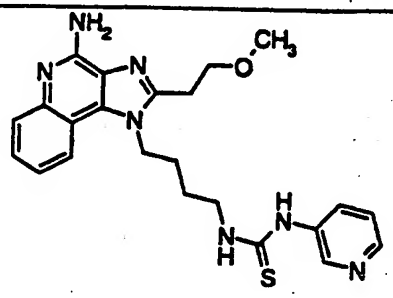
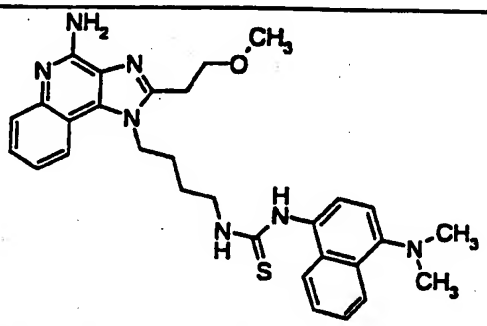
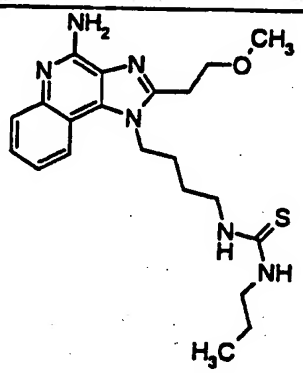
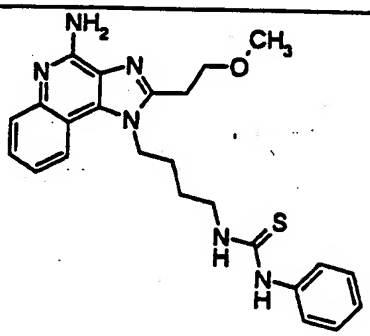
imidazo[4,5-*c*]quinolin-4-amine with the appropriate isocyanate using the general method of Examples 53 - 66 above.

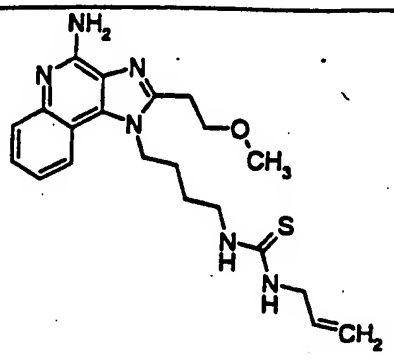
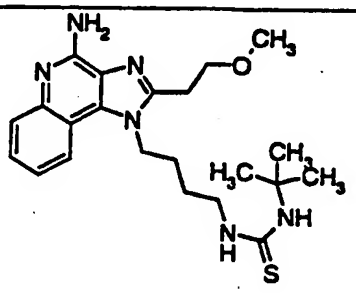
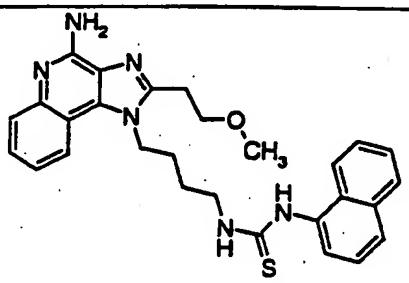
Example #	Structure of the Free Base	Mass
123		461.3
124		495.3

Examples 125 - 131

The examples in the table below were prepared according to the synthetic method of Reaction Scheme II above using the following method. 1-(4-Aminobutyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-c]quinolin-4-amine (50 mg), dichloromethane (2 mL) and the thioisocyanate (1.1 eq) were placed in a 2 dram (7.4 mL) vial. The vial was placed on a sonicator for about 30-60 minutes at ambient temperature. The reaction mixture was analyzed by LC/MS to confirm the formation of the desired product. The solvent was removed and the residue was purified by semi-preparative HPLC (Capcell Pak C18 column, 35 mm x 20 mm, 5 micron particle size, 20 mL/min., gradient elution from 5-95% B in 10 min., hold at 95% B for 2 min., where A=0.1 % trifluoroacetic acid/water and B=0.1 % trifluoroacetic acid/acetonitrile, peak detection at 254 nm for triggering fraction collection). The semi-prep HPLC fractions were analyzed by LC-APCI/MS and the

appropriate fractions were combined and lyophilized to provide the trifluoroacetate salt of the desired thiourea.

Example #	Structure of the Free Base	Mass
125		450.1
126		542.2
127		415.1
128		449.1

Example #	Structure of the Free Base	Mass
129		413.1
130		429.2
131		499.2

Examples 132 - 137

The examples in the table below were prepared according to the synthetic route shown in Reaction Scheme VII above.

Part A

The tetrahydroquinoline amine starting materials were prepared as follows.

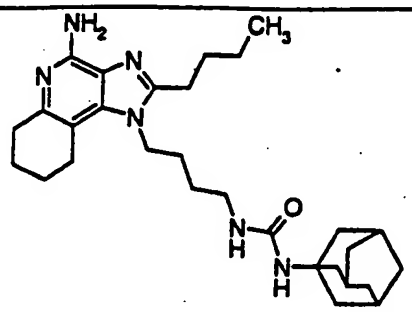
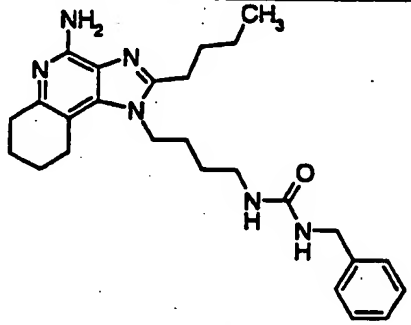
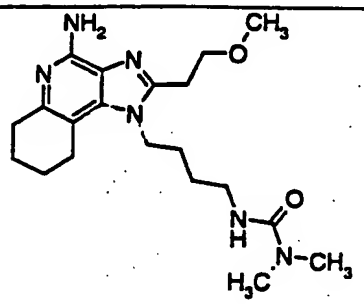
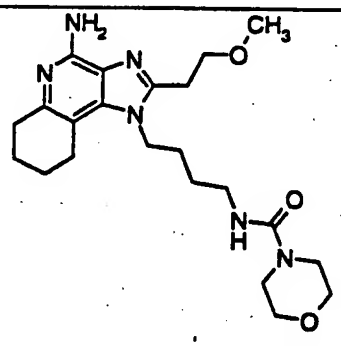
A catalytic amount of platinum (IV) oxide was added to a solution of 1-(4-aminobutyl)-2-butyl-1*H*-imidazo[4,5-c]quinolin-4-amine (2.2 g, 7.06 mmol) in trifluoroacetic acid (200 mL). The reaction mixture was hydrogenated at 50 psi (3.44 X 10^5 Pa) on a Parr apparatus for 6 days.. The reaction mixture was filtered to remove the catalyst and the filtrate was concentrated under vacuum. The residue was combined with 1 N hydrochloric acid (100 mL) and heated on a steam bath for 2 hours. The mixture was

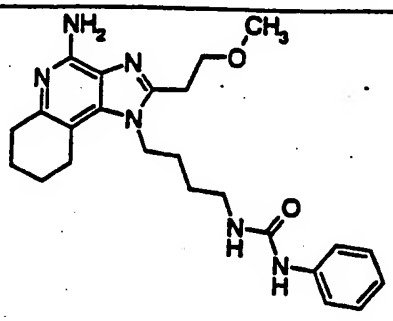
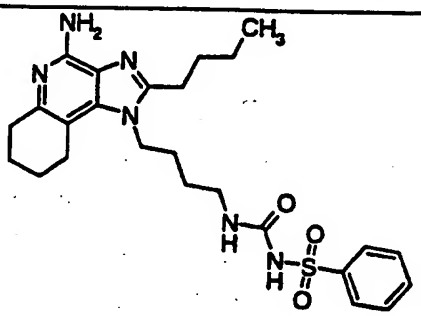
cooled, made basic with ammonium hydroxide and then extracted with dichloromethane. The extract was concentrated under vacuum to provide of 1-(4-aminobutyl)-2-butyl-6,7,8,9-tetrahydro -1*H*-imidazo[4,5-c]quinolin-4-amine as a solid, m.p. 63-67°C

A catalytic amount of platinum (IV) oxide was added to a solution of 1-(4-aminobutyl)-2-methoxyethyl-1*H*-imidazo[4,5-c]quinolin-4-amine (7.7 g, 24.5 mmol) in trifluoroacetic acid (250 mL). The reaction mixture was hydrogenated at 50 psi (3.44 X 10^5 Pa) on a Parr apparatus. The progress of the reaction was monitored by LC/MS. Additional catalyst was added 7, 11, and 17 days after the start of the reaction. After 25 days the reaction was complete. The reaction mixture was filtered through a layer of Celite® filter aid to remove the catalyst and the filtrate was concentrated under vacuum. The residue was combined with 1 N hydrochloric acid (100 mL) and stirred overnight. The mixture was made basic (pH = 11) with ammonium hydroxide and then extracted with dichloromethane (3 X 300 mL). The extracts were combined and concentrated under vacuum to provide 3.5 g of 1-(4-aminobutyl)-6,7,8,9-tetrahydro-2-methoxyethyl-1*H*-imidazo[4,5-c]quinolin-4-amine as a solid.

Part B

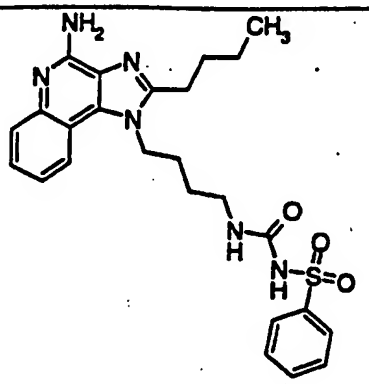
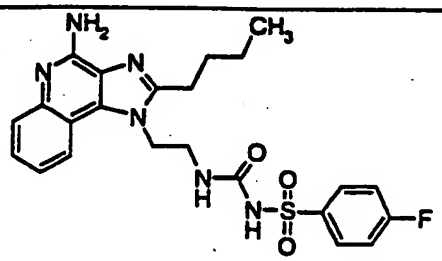
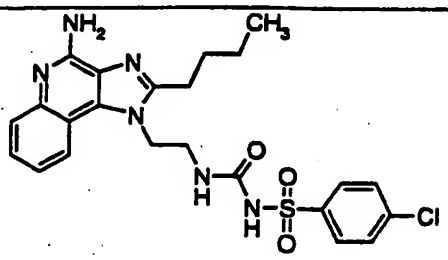
The tetrahydroimidazoquinoline amines from Part A were reacted with the appropriate isocyanate or sulfonyl isocyanate using the general method of Examples 53 - 66 above to provide the trifluoroacetate salt of the desired urea or sulfonyl urea.

Example #	Structure of the Free Base	Mass
132		493.20
133		449.2
134		389.2
135		431.2

Example #	Structure of the Free Base	Mass
136		437.2
137		499.1

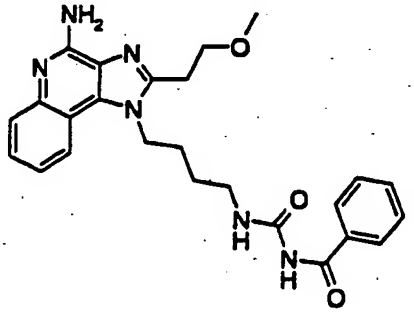
Examples 138 - 140

The examples in the table below were prepared according to the synthetic method of Reaction Scheme VI above using the following procedure. The 1*H*-imidazo[4,5-c]quinolin-4-amine (50 mg), dichloromethane (2 mL) and the sulfonylisocyanate (1.3 eq) were placed in a 2 dram (7.4 mL) vial. The vial was placed on a shaker at ambient temperature. The reaction mixture was analyzed by LC/MS to confirm the formation of the desired product. The solvent was removed and the residue was purified by semi-preparative HPLC (Capcell Pak C18 column, 35 mm x 20 mm, 5 micron particle size, 20 mL/min., gradient elution from 5-95% B in 10 min., hold at 95% B for 2 min., where A=0.1 % trifluoroacetic acid/water and B=0.1 % trifluoroacetic acid/acetonitrile, peak detection at 254 nm for triggering fraction collection). The semi-prep HPLC fractions were analyzed by LC-APCI/MS and the appropriate fractions were combined and lyophilized to provide the trifluoroacetate salt of the desired sulfonylurea.

Example #	Structure of the Free Base	Mass
138		495.2
139		485.0
140		501.0, 503.0

Example 141

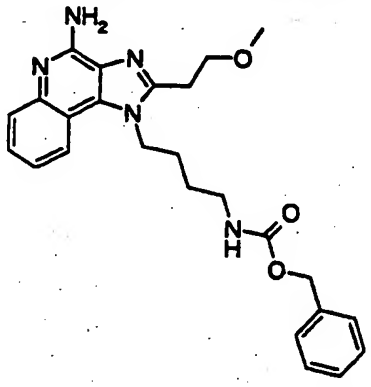
N^1-{4-[4-Amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-N^3-benzoylurea Trifluoroacetate



This compound was prepared according to the synthetic method of Reaction Scheme V above. The 1-(4-aminobutyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-c]quinolin-4-amine (50 mg), dichloromethane (2 mL) and benzoylisocyanate (1.1 eq) were placed in a 2 dram (7.4 mL) vial. The vial was placed on a shaker for 2 hours at ambient temperature. The reaction mixture was analyzed by LC/MS to confirm the formation of the desired product. The solvent was removed and the residue was purified by semi-preparative HPLC (Capcell Pak C18 column, 35 mm x 20 mm, 5 micron particle size, 20 mL/min., gradient elution from 5-95% B in 10 min., hold at 95% B for 2 min., where A=0.1 % trifluoroacetic acid/water and B=0.1 % trifluoroacetic acid/acetonitrile, peak detection at 254 nm for triggering fraction collection). The semi-prep HPLC fractions were analyzed by LC-APCI/MS and the appropriate fractions were combined and lyophilized to provide the trifluoroacetate salt of the desired compound. MS (APCI) m/e 461.2 (M+H).

Example 142

N-{4-[4-Amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl} carbamate Trifluoroacetate



This compound was prepared according to the synthetic method of Reaction Scheme IV above. The 1-(4-aminobutyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-c]quinolin-4-amine (50 mg), diisopropylethylamine (1.2 eq.), dichloromethane (2 mL) and benzyl chloroformate (1.1 eq) were placed in a 2 dram (7.4 mL) vial. The vial was placed on a shaker for 2 hours at ambient temperature. The reaction mixture was analyzed by LC/MS to confirm the formation of the desired product. The solvent was removed and the residue was purified by semi-preparative HPLC (Capcell Pak C18 column, 35 mm x 20 mm, 5

micron particle size, 20 mL/min., gradient elution from 5-95% B in 10 min., hold at 95% B for 2 min., where A=0.1 % trifluoroacetic acid/water and B=0.1 % trifluoroacetic acid/acetonitrile, peak detection at 254 nm for triggering fraction collection). The semi-prep HPLC fractions were analyzed by LC-APCI/MS and the appropriate fractions were combined and lyophilized to provide the trifluoroacetate salt of the desired compound. MS (APCI) m/e 448.2 (M+H).

CYTOKINE INDUCTION IN HUMAN CELLS

An in vitro human blood cell system was used to assess cytokine induction by compounds of the invention. Activity is based on the measurement of interferon and tumor necrosis factor (α) (IFN and TNF, respectively) secreted into culture media as described by Testerman et. al. In "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", Journal of Leukocyte Biology, 58, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood is collected by venipuncture into EDTA vacutainer tubes from healthy human donors. Peripheral blood mononuclear cells (PBMCs) are separated from whole blood by density gradient centrifugation using Histopaque®-1077 (Sigma Chemicals, St. Louis, MO). The PBMCs are suspended at 3-4 x 10^6 cells/mL in RPMI 1640 medium containing 10 % fetal bovine serum, 2 mM L-glutamine and 1% penicillin/streptomycin solution (RPMI complete). The PBMC suspension is added to 48 well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson Labware, Lincoln Park, NJ) containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells.

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial (three fold or ten fold) dilutions are made. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range. The final concentration of PBMC suspension is 1.5–2 X 10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 5-10 minutes at 1000 rpm (~200 x g) at 4°C. The cell culture supernatant is removed with a sterile polypropylene pipet and transferred to sterile polypropylene tubes. Samples are maintained at –30 to -70°C until analysis. The samples are analyzed for interferon (α) and tumor necrosis factor (α) by ELISA

Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA

Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ.

Tumor necrosis factor (α) (TNF)concentration is determined using ELISA kits available from Genzyme, Cambridge, MA; R&D Systems, Minneapolis, MN; or Pharmingen, San Diego, CA.

The table below lists the lowest concentration found to induce interferon and the lowest concentration found to induce tumor necrosis factor for each compound. A "**" indicates that no induction was seen at any of the tested concentrations (0.12, 0.37, 1.11, 3.33, 10 and 30 μM). A "***" indicates that no induction was seen at any of the tested concentrations (0.0001, 0.001, 0.01, 0.1, 1 and 10 μM).

Cytokine Induction in Human Cells		
Example Number	Lowest Effective Concentration (μM)	
	Interferon	Tumor Necrosis Factor
2	0.37	3.33
16	1.11	10

Cytokine Induction in Human Cells		
Example Number	Lowest Effective Concentration (μM)	
	Interferon	Tumor Necrosis Factor
2	0.37	3.33
4	**	**
17	**	30
19	1.11	30
20	1.11	30
21	**	**
22	**	10
23	**	10
24	**	**
25	3.33	**
26	10	**
27	**	**
28	1.11	3.33
29	**	10
30	3.33	30
31	**	10
32	10	10
33	**	**
34	**	**
35	1.11	10
36	1.11	10
37	1.11	10
38	**	**
39	1.11	10
40	0.37	3.33
41	1.11	10
42	**	**
43	**	**

Cytokine Induction in Human Cells		
Example Number	Lowest Effective Concentration (μM)	
	Interferon	Tumor Necrosis Factor
44	1.11	10
45	3.33	**
46	1.11	3.33
1	3.33	30
47	3.33	10
48	0.37	3.33
49	3.33	3.33
50	**	**
51	30	30
52	1.11	10
6	0.37	**
5	3.33	**
67	1	10
69	0.1	1
68	1	1
137	1	10
132	0.01	1
133	0.1	10
53	***	10
54	***	10
55	1	1
56	1	1
139	***	***
140	10	***
100	0.001	10
125	0.0001	10
126	0.0001	1
127	0.0001	1

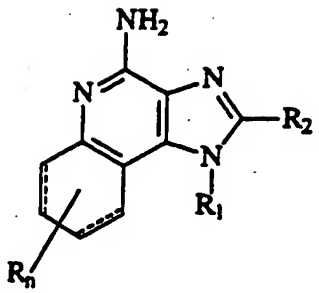
Cytokine Induction in Human Cells		
Example Number	Lowest Effective Concentration (μM)	
	Interferon	Tumor Necrosis Factor
120	0.0001	0.01
121	0.01	10
122	0.001	1
71	0.001	1
81	0.01	1
82	0.01	0.1
83	0.1	1
84	0.1	1
85	0.001	0.1
86	0.1	1
87	1	***
88	0.1	1
89	0.1	10
101	0.01	1
102	0.001	1
103	0.0001	0.1
104	0.0001	1
105	0.001	1
106	0.0001	1
107	0.0001	1
108	0.0001	0.0001
109	0.0001	0.1
141	***	10
110	0.001	1
111	0.001	1
112	0.0001	0.1
113	0.0001	1
114	0.0001	0.01

Cytokine Induction in Human Cells		
Example Number	Lowest Effective Concentration (μM)	
	Interferon	Tumor Necrosis Factor
115	0.0001	1
116	0.0001	1
117	10	10
118	10	10
119	10	10
142	0.0001	0.1
134	0.001	1
135	0.01	10
136	0.0001	1

The present invention has been described with reference to several embodiments thereof. The foregoing detailed description and examples have been provided for clarity of understanding only, and no unnecessary limitations are to be understood therefrom. It will be apparent to those skilled in the art that many changes can be made to the described embodiments without departing from the spirit and scope of the invention. Thus, the scope of the invention should not be limited to the exact details of the compositions and structures described herein, but rather by the language of the claims that follow.

WHAT IS CLAIMED IS:

1. A compound of the formula (I):



(I)

wherein

R_1 is -alkyl-NR_3-CY-NR_5-X-R_4 or -alkenyl-NR_3-CY- NR_5-X- R_4 wherein

Y is =O or =S;

X is a bond, -CO- or $-SO_2-$;

R_4 is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of:

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-substituted aryl;

-substituted heteroaryl;

-substituted heterocyclyl;

-O-alkyl;

-O-$(alkyl)_{0-1}$-aryl;

-O-$(alkyl)_{0-1}$-substituted aryl;

-O-$(alkyl)_{0-1}$-heteroaryl;

-O-$(alkyl)_{0-1}$-substituted heteroaryl;

-O-(alkyl)$_{0-1}$-heterocyclyl;

-O-(alkyl)$_{0-1}$-substituted heterocyclyl;

-COOH;

-CO-O-alkyl;

-CO-alkyl;

-S(O)$_{0-2}$-alkyl;

-S(O)$_{0-2}$–(alkyl)$_{0-1}$-aryl;

-S(O)$_{0-2}$–(alkyl)$_{0-1}$-substituted aryl;

-S(O)$_{0-2}$–(alkyl)$_{0-1}$-heteroaryl;

-S(O)$_{0-2}$–(alkyl)$_{0-1}$-substituted heteroaryl;

-S(O)$_{0-2}$–(alkyl)$_{0-1}$-heterocyclyl;

-S(O)$_{0-2}$–(alkyl)$_{0-1}$-substituted heterocyclyl;

-(alkyl)$_{0-1}$-NR_3R_3;

-(alkyl)$_{0-1}$-NR_3-CO-O-alkyl;

-(alkyl)$_{0-1}$-NR_3-CO-alkyl;

-(alkyl)$_{0-1}$-NR_3-CO-aryl;

-(alkyl)$_{0-1}$-NR_3-CO-substituted aryl;

-(alkyl)$_{0-1}$-NR_3-CO-heteroaryl;

-(alkyl)$_{0-1}$-NR_3-CO-substituted heteroaryl;

-N_3;

-halogen;

-haloalkyl;

-haloalkoxy;

-CO-haloalkoxy;

-NO_2;

-CN;

-OH;

-SH; and, in the case of alkyl, alkenyl or heterocyclyl, oxo;

with the proviso that when X is a bond R_4 can additionally be hydrogen;

R_2 is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

- alkyl -O-alkyl;

-alkyl-O- alkenyl; and

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

-$N(R_3)_2$;

-$CO\text{-}N(R_3)_2$;

-$CO\text{-}C_{1\text{-}10}$ alkyl;

-$CO\text{-}O\text{-}C_{1\text{-}10}$ alkyl;

-N_3;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-heterocyclyl;

-substituted heterocyclyl;

-CO-aryl;

-CO-(substituted aryl);

-CO-heteroaryl; and

-CO-(substituted heteroaryl);

each R_3 is independently selected from the group consisting of hydrogen and $C_{1\text{-}10}$ alkyl;

R_5 is selected from the group consisting of hydrogen and $C_{1\text{-}10}$ alkyl, or R_4 and R_5 can combine to form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;

n is 0 to 4 and each R present is independently selected from the group consisting of $C_{1\text{-}10}$ alkyl, $C_{1\text{-}10}$ alkoxy, halogen and trifluoromethyl,

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 wherein X is a bond and Y is =O.

3. A compound of claim 2 wherein n is 0.

4. A compound of claim 2 wherein R_3 is hydrogen.

5. A compound of claim 2 wherein R_1 is $-(CH_2)_{2-4}-NR_3-CO-NR_5-R_4$.

6. A compound of claim 2 wherein R_2 is selected from the group consisting of hydrogen; alkyl; alkyl-O-alkyl; $(alkyl)_{0-1}$ aryl, $(alkyl)_{0-1}$-(substituted aryl); $(alkyl)_{0-1}$-heteroaryl; and $(alkyl)_{0-1}$-(substituted heteroaryl).

7. A compound of claim 2 wherein R_2 is selected from the group consisting of hydrogen, C_{1-4}alkyl, and C_{1-4}alkyl-O- C_{1-4}alkyl.

8. A compound of claim 2 wherein R_4 is alkyl, phenyl or pyridyl, which may be unsubstituted or substituted by one or more substituents selected from the group consisting of:

-alkyl;
-alkenyl;
-aryl;
-heteroaryl;
-heterocyclyl;
-substituted aryl;
-substituted heteroaryl;
-substituted heterocyclyl;
-O-alkyl;
-O-$(alkyl)_{0-1}$-aryl;
-O-$(alkyl)_{0-1}$-substituted aryl;
-O-$(alkyl)_{0-1}$-heteroaryl;

-O-(alkyl)$_{0-1}$-substituted heteroaryl;

-O-(alkyl)$_{0-1}$-heterocyclyl;

-O-(alkyl)$_{0-1}$-substituted heterocyclyl;

-COOH;

-CO-O-alkyl;

-CO-alkyl;

-S(O)$_{0-2}$-alkyl;

-S(O)$_{0-2}$–(alkyl)$_{0-1}$-aryl;

-S(O)$_{0-2}$–(alkyl)$_{0-1}$-substituted aryl;

-S(O)$_{0-2}$–(alkyl)$_{0-1}$-heteroaryl;

-S(O)$_{0-2}$–(alkyl)$_{0-1}$-substituted heteroaryl;

-S(O)$_{0-2}$–(alkyl)$_{0-1}$-heterocyclyl;

-S(O)$_{0-2}$–(alkyl)$_{0-1}$-substituted heterocyclyl;

-(alkyl)$_{0-1}$-NR_3R_3;

-(alkyl)$_{0-1}$-NR_3-CO-O-alkyl;

-(alkyl)$_{0-1}$-NR_3-CO-alkyl;

-(alkyl)$_{0-1}$-NR_3-CO-aryl;

-(alkyl)$_{0-1}$-NR_3-CO-substituted aryl;

-(alkyl)$_{0-1}$-NR_3-CO-heteroaryl;

-(alkyl)$_{0-1}$-NR_3-CO-substituted heteroaryl;

-N_3;

-halogen;

-haloalkyl;

-haloalkoxy;

-CO-haloalkoxy;

-NO_2;

-CN;

-OH;

-SH; and, in the case of alkyl, oxo.

9. A compound of claim 2 wherein R_4 is phenyl that is unsubstituted or substituted by one or more substituents selected from the group consisting of methyl, methoxy, halogen, nitrile, nitro, trifluoromethyl, and trifluoromethoxy.

10. A compound of claim 2 wherein R_4 and R_5 combine to form a 3 to 7 membered substituted or unsubstituted heterocyclic ring.

11. A compound of claim 2 wherein R_4 and R_5 combine to form a substituted or unsubstituted pyrrolidine or morpholine ring.

12. A compound of claim 1 wherein X is a bond and Y is =S.

13. A compound of claim 12 wherein n is 0.

14. A compound of claim 12 wherein R_3 is hydrogen.

15. A compound of claim 12 wherein R_1 is $-(CH_2)_{2-4}- NR_3- CO-NR_5 -R_4$.

16. A compound of claim 12 wherein R_2 is selected from the group consisting of hydrogen; alkyl; alkyl-O-alkyl; $(alkyl)_{0-1}$ aryl, $(alkyl)_{0-1}$-(substituted aryl); $(alkyl)_{0-1}$-heteroaryl; and $(alkyl)_{0-1}$-(substituted heteroaryl).

17. A compound of claim 12 wherein R_2 is selected from the group consisting of hydrogen, C_{1-4}alkyl, and C_{1-4}alkyl-O- C_{1-4}alkyl.

18. A compound of claim 12 wherein R_4 is alkyl, phenyl, or pyridyl, which may be unsubstituted or substituted by one or more substituents selected from the group consisting of:

-alkyl;
-alkenyl;
-aryl;
-heteroaryl;

-heterocyclyl;
-substituted aryl;
-substituted heteroaryl;
-substituted heterocyclyl;
-O-alkyl;
-O-(alkyl)$_{0-1}$-aryl;
-O-(alkyl)$_{0-1}$-substituted aryl;
-O-(alkyl)$_{0-1}$-heteroaryl;
-O-(alkyl)$_{0-1}$-substituted heteroaryl;
-O-(alkyl)$_{0-1}$-heterocyclyl;
-O-(alkyl)$_{0-1}$-substituted heterocyclyl;
-COOH;
-CO-O-alkyl;
-CO-alkyl;
-S(O)$_{0-2}$-alkyl;
-S(O)$_{0-2}$–(alkyl)$_{0-1}$-aryl;
-S(O)$_{0-2}$–(alkyl)$_{0-1}$-substituted aryl;
-S(O)$_{0-2}$–(alkyl)$_{0-1}$-heteroaryl;
-S(O)$_{0-2}$–(alkyl)$_{0-1}$-substituted heteroaryl;
-S(O)$_{0-2}$–(alkyl)$_{0-1}$-heterocyclyl;
-S(O)$_{0-2}$–(alkyl)$_{0-1}$-substituted heterocyclyl;
-(alkyl)$_{0-1}$-NR_3R_3;
-(alkyl)$_{0-1}$-NR_3-CO-O-alkyl;
-(alkyl)$_{0-1}$-NR_3-CO-alkyl;
-(alkyl)$_{0-1}$-NR_3-CO-aryl;
-(alkyl)$_{0-1}$-NR_3-CO-substituted aryl;
-(alkyl)$_{0-1}$-NR_3-CO-heteroaryl;
-(alkyl)$_{0-1}$-NR_3-CO-substituted heteroaryl;
-N_3;
-halogen;
-haloalkyl;
-haloalkoxy;

-CO-haloalkoxy;

$-NO_2$;

-CN;

-OH;

-SH; and, in the case of alkyl, oxo.

19. A compound of claim 12 wherein R_4 is phenyl that is unsubstituted or substituted by one or more substituents selected from the group consisting of methyl, methoxy, halogen, nitrile, nitro, trifluoromethyl, and trifluoromethoxy.

20. A compound of claim 12 wherein R_4 and R_5 combine to form a 3 to 7 membered substituted or unsubstituted heterocyclic ring.

21. A compound of claim 12 wherein R_4 and R_5 combine to form a substituted or unsubstituted pyrrolidine or morpholine ring.

22. A compound of claim 1 wherein X is a bond and R_4 is hydrogen.

23. A compound of claim 1 wherein Y is = O and X is –CO-.

24. A compound of claim 23 wherein n is 0.

25. A compound of claim 23 wherein R_3 is hydrogen.

26. A compound of claim 23 wherein R_1 is $-(CH_2)_{2-4}- NR_3- CO-NR_5-CO-R_4$.

27. A compound of claim 23 wherein R_2 is selected from the group consisting of hydrogen; alkyl; alkyl-O-alkyl; $(alkyl)_{0-1}$ aryl, $(alkyl)_{0-1}$-(substituted aryl); $(alkyl)_{0-1}$-heteroaryl; and $(alkyl)_{0-1}$-(substituted heteroaryl).

28. A compound of claim 23 wherein R_2 is selected from the group consisting of hydrogen, C_{1-4}alkyl, and C_{1-4}alkyl-O- C_{1-4}alkyl.

29. A compound of claim 23 wherein R_4 is alkyl, phenyl, or pyridyl, which may be unsubstituted or substituted by one or more substituents selected from the group consisting of:

-alkyl;
-alkenyl;
-aryl;
-heteroaryl;
-heterocyclyl;
-substituted aryl;
-substituted heteroaryl;
-substituted heterocyclyl;
-O-alkyl;
-O-$(alkyl)_{0-1}$-aryl;
-O-$(alkyl)_{0-1}$-substituted aryl;
-O-$(alkyl)_{0-1}$-heteroaryl;
-O-$(alkyl)_{0-1}$-substituted heteroaryl;
-O-$(alkyl)_{0-1}$-heterocyclyl;
-O-$(alkyl)_{0-1}$-substituted heterocyclyl;
-COOH;
-CO-O-alkyl;
-CO-alkyl;
-$S(O)_{0-2}$-alkyl;
-$S(O)_{0-2}$-$(alkyl)_{0-1}$-aryl;
-$S(O)_{0-2}$-$(alkyl)_{0-1}$-substituted aryl;
-$S(O)_{0-2}$-$(alkyl)_{0-1}$-heteroaryl;
-$S(O)_{0-2}$-$(alkyl)_{0-1}$-substituted heteroaryl;
-$S(O)_{0-2}$-$(alkyl)_{0-1}$-heterocyclyl;
-$S(O)_{0-2}$-$(alkyl)_{0-1}$-substituted heterocyclyl;
-$(alkyl)_{0-1}$-NR_3R_3;
-$(alkyl)_{0-1}$-NR_3-CO-O-alkyl;
-$(alkyl)_{0-1}$-NR_3-CO-alkyl;

-(alkyl)$_{0-1}$-NR_3-CO-aryl;
-(alkyl)$_{0-1}$-NR_3-CO-substituted aryl;
-(alkyl)$_{0-1}$-NR_3-CO-heteroaryl;
-(alkyl)$_{0-1}$-NR_3-CO-substituted heteroaryl;
-N_3;
-halogen;
-haloalkyl;
-haloalkoxy;
-CO-haloalkoxy;
-NO_2;
-CN;
-OH;
-SH; and, in the case of alkyl, oxo.

30. A compound of claim 23 wherein R_4 is phenyl that is unsubstituted or substituted by one or more substituents selected from the group consisting of methyl, methoxy, halogen, nitrile, nitro, trifluoromethyl, and trifluoromethoxy.

31. A compound of claim 23 wherein R_4 and R_5 combine to form a 3 to 7 membered substituted or unsubstituted heterocyclic ring.

32. A compound of claim 23 wherein R_4 and R_5 combine to form a substituted or unsubstituted pyrrolidine or morpholine ring.

33. A compound of claim 1 wherein Y is=O and X is $-SO_2-$.

34. A compound of claim 33 wherein n is 0.

35. A compound of claim 33 wherein R_3 is hydrogen.

36. A compound of claim 33 wherein R_1 is $-(CH_2)_{2-4}-$ NR_3-CO-NR_5 $-SO_2-R_4$.

37. A compound of claim 33 wherein R_2 is selected from the group consisting of hydrogen; alkyl; alkyl-O-alkyl; $(alkyl)_{0-1}$ aryl, $(alkyl)_{0-1}$-(substituted aryl); $(alkyl)_{0-1}$-heteroaryl; and $(alkyl)_{0-1}$-(substituted heteroaryl).

38. A compound of claim 33 wherein R_2 is selected from the group consisting of hydrogen, C_{1-4}alkyl, and C_{1-4}alkyl-O- C_{1-4}alkyl.

39. A compound of claim 33 wherein R_4 is alkyl or phenyl, which may be unsubstituted or substituted by one or more substituents selected from the group consisting of:

-alkyl;
-alkenyl;
-aryl;
-heteroaryl;
-heterocyclyl;
-substituted aryl;
-substituted heteroaryl;
-substituted heterocyclyl;
-O-alkyl;
-O-$(alkyl)_{0-1}$-aryl;
-O-$(alkyl)_{0-1}$-substituted aryl;
-O-$(alkyl)_{0-1}$-heteroaryl;
-O-$(alkyl)_{0-1}$-substituted heteroaryl;
-O-$(alkyl)_{0-1}$-heterocyclyl;
-O-$(alkyl)_{0-1}$-substituted heterocyclyl;
-COOH;
-CO-O-alkyl;
-CO-alkyl;
-$S(O)_{0-2}$-alkyl;
-$S(O)_{0-2}$–$(alkyl)_{0-1}$-aryl;
-$S(O)_{0-2}$–$(alkyl)_{0-1}$-substituted aryl;
-$S(O)_{0-2}$–$(alkyl)_{0-1}$-heteroaryl;

-$S(O)_{0-2}$–(alkyl)$_{0-1}$-substituted heteroaryl;
-$S(O)_{0-2}$–(alkyl)$_{0-1}$-heterocyclyl;
-$S(O)_{0-2}$–(alkyl)$_{0-1}$-substituted heterocyclyl;
-(alkyl)$_{0-1}$-NR_3R_3;
-(alkyl)$_{0-1}$-NR_3-CO-O-alkyl;
-(alkyl)$_{0-1}$-NR_3-CO-alkyl;
-(alkyl)$_{0-1}$-NR_3-CO-aryl;
-(alkyl)$_{0-1}$-NR_3-CO-substituted aryl;
-(alkyl)$_{0-1}$-NR_3-CO-heteroaryl;
-(alkyl)$_{0-1}$-NR_3-CO-substituted heteroaryl;
-N_3;
-halogen;
-haloalkyl;
-haloalkoxy;
-CO-haloalkoxy;
-NO_2;
-CN;
-OH;
-SH; and, in the case of alkyl, oxo.

40. A compound of claim 33 wherein R_4 is phenyl that is unsubstituted or substituted by one or more substituents selected from the group consisting of methyl, methoxy, halogen, nitrile, nitro, trifluoromethyl, and trifluoromethoxy.

41. A compound of claim 33 wherein R_4 and R_5 combine to form a 3 to 7 membered substituted or unsubstituted heterocyclic ring.

42. A compound of claim 33 wherein R_4 and R_5 combine to form a substituted or unsubstituted pyrrolidine or morpholine ring.

43. A compound of claim 1 wherein the dashed bonds are absent.

44. A compound of claim 2 wherein the dashed bonds are absent.

45. A compound of claim 12 wherein the dashed bonds are absent.

46. A compound of claim 23 wherein the dashed bonds are absent.

47. A compound of claim 33 wherein the dashed bonds are absent.

48. A compound selected from the group consisting of:

N-[4-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-N'-benzylurea;
N-[4-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-N'-butylurea;
N-[4-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-N'-(2-ethylphenyl)urea;
N-[4-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-N'-cyclohexylurea;
N'-[4-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-N-methyl-N-phenylurea;
N-[2-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]-N'-phenylurea;
N-[2-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]-N'-(4-phenoxyphenyl)urea;
N-[2-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]-N'-benzylurea;
N-[2-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]-N'-propylurea;
N-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-N'-propylurea;
N{-2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-N'-phenylurea;
N-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-N'-cyclohexylurea;
N-{2-[4-amino-2-(ethoxymethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-N'-cyclohexylurea;
N-{2-[4-amino-2-(ethoxymethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-N'-phenylurea;
N-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-N'-propylurea;
N-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-N'-[(1S)-1-

phenylethyl]urea;

N-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-N'-[(1R)-1-phenylethyl]urea;

N-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-N'-(2-methoxyphenyl)urea;

N-(4-acetylphenyl)-N'-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]urea;

N-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-N'-[4-(dimethylamino)phenyl]urea;

N-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-N'-(4-methoxybenzyl)urea;

N-{4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-N'-propylurea;

N-{4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-N'-phenylurea;

N-{4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-N'-cyclohexylurea;

N-{4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl]-N'-(3-methylphenyl)urea;

N-{4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-N'-(3-fluorophenyl)urea;

N4-4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl-4-morpholinecarboxamide;

N-{4-[4-amino-2-(4-methoxybenzyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-N'-propylurea;

N-{4-[4-amino-2-(4-methoxybenzyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-N'-phenylurea; and

N-{4-[4-amino-2-(4-methoxybenzyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-N'-(3-pyridyl)urea.

49. A compound selected from the group consisting of:

N-[4-(4-amino-2-butyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-N'-benzylurea;

N'-{4-[4-amino-2-(2-methoxyethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-N,N-dimethylurea;

N^4-{4-[4-amino-2-(2-methoxyethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-4-morpholinecarboxamide; and

N-{4-[4-amino-2-(2-methoxyethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-N'-phenylurea.

50. A compound selected from the group consisting of:

N-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl}-N'-cyclohexylthiourea;

N-[4-(4-amino-2-butyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-N'-cyclohexylthiourea;

N-{4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-N'-(3-pyridyl)thiourea;

N-{4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-N'-(4-(dimethylamino)-1-naphthyl)thiourea;

N-{4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-N'-propylthiourea;

N-{4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-N'-phenylthiourea;

N-{4-[4-amino-2-(2-methoxyethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-N'-phenylthiourea;

N-allyl-N'-{4-[4-amino-2-(2-methoxyethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}thiourea;

N-{4-[4-amino-2-(2-methoxyethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-N'-(tert-butyl)thiourea;

N-{4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-N'-(1-naphthyl)thiourea;

N-{4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-

N'-(tert-butyl)thiourea; and

N-allyl-N'-{4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}thiourea.

51. A compound selected from the group consisting of:

4-amino-2-butyl-1-[4-({[(phenylsulfonyl)amino]carbonyl}amino)butyl]-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline;

4-amino-2-butyl-1-[4-({[(phenylsulfonyl)amino]carbonyl}amino)butyl]-1*H*-imidazo[4,5-*c*]quinoline;

4-amino-2-butyl-1-{4-[({[(4-fluorophenyl)sulfonyl]amino}carbonyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinoline;

4-amino-2-butyl-1-{4-[({[(4-chlorophenyl)sulfonyl]amino}carbonyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinoline;

4-amino-2-butyl-1-{4-[({[(4-ethylphenyl)sulfonyl]amino}carbonyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinoline;

4-amino-2-(2-methoxyethyl)-1-{4-[({[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinoline;

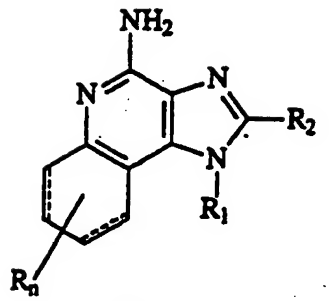
4-amino-2-(2-methoxyethyl)-1-[4-({[(phenylsulfonyl)amino]carbonyl}amino)butyl]-1*H*-imidazo[4,5-*c*]quinoline;

4-amino-2-(ethoxymethyl)-1-[2-({[(phenylsulfonyl)amino]carbonyl}amino)ethyl]-1*H*-imidazo[4,5-*c*]quinoline;

4-amino-2-butyl-1-{2-[({[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}-1*H*-imidazo[4,5-*c*]quinoline; and

4-amino-2-butyl-1-{2-[({[(4-chlorophenyl)sulfonyl]amino}carbonyl)amino]ethyl}-1*H*-imidazo[4,5-*c*]quinoline.

52. A pharmaceutical composition comprising a therapeutically effective amount of a compound of the formula Ia:



(Ia)

wherein

R_1 is -alkyl-NR_3-CO-O-R_4 or -alkenyl-NR_3-CO- O- R_4;

R_4 is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of:

-alkyl;
-alkenyl;
-aryl;
-heteroaryl;
-heterocyclyl;
-substituted aryl;
-substituted heteroaryl;
-substituted heterocyclyl;
-O-alkyl;
-O-$(alkyl)_{0-1}$-aryl;
-O-$(alkyl)_{0-1}$-substituted aryl;
-O-$(alkyl)_{0-1}$-heteroaryl;
-O-$(alkyl)_{0-1}$-substituted heteroaryl;
-O-$(alkyl)_{0-1}$-heterocyclyl;
-O-$(alkyl)_{0-1}$-substituted heterocyclyl;
-COOH;
-CO-O-alkyl;
-CO-alkyl;
-$S(O)_{0-2}$-alkyl;

-$S(O)_{0-2}$–(alkyl)$_{0-1}$-aryl;

-$S(O)_{0-2}$–(alkyl)$_{0-1}$-substituted aryl;

-$S(O)_{0-2}$–(alkyl)$_{0-1}$-heteroaryl;

-$S(O)_{0-2}$–(alkyl)$_{0-1}$-substituted heteroaryl;

-$S(O)_{0-2}$–(alkyl)$_{0-1}$-heterocyclyl;

-$S(O)_{0-2}$–(alkyl)$_{0-1}$-substituted heterocyclyl;

-(alkyl)$_{0-1}$-NR_3R_3;

-(alkyl)$_{0-1}$-NR_3-CO-O-alkyl;

-(alkyl)$_{0-1}$-NR_3-CO-alkyl;

-(alkyl)$_{0-1}$-NR_3-CO-aryl;

-(alkyl)$_{0-1}$-NR_3-CO-substituted aryl;

-(alkyl)$_{0-1}$-NR_3-CO-heteroaryl;

-(alkyl)$_{0-1}$-NR_3-CO-substituted heteroaryl;

-N_3;

-halogen;

-haloalkyl;

-haloalkoxy;

-CO-haloalkoxy;

-NO_2;

-CN;

-OH;

-SH; and, in the case of alkyl, alkenyl, or heterocyclyl, oxo;

R_2 is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

- alkyl -O-alkyl;

-alkyl-O- alkenyl; and

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

-$N(R_3)_2$;

-CO-$N(R_3)_2$;

-CO-C_{1-10} alkyl;

-CO-O-C_{1-10} alkyl;

-N_3;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-heterocyclyl;

-substituted heterocyclyl;

-CO-aryl;

-CO-(substituted aryl);

-CO-heteroaryl; and

-CO-(substituted heteroaryl);

each R_3 is independently selected from the group consisting of hydrogen and C_{1-10} alkyl;

n is 0 to 4 and each R present is independently selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkoxy, halogen and trifluoromethyl,

or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

53. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 in combination with a pharmaceutically acceptable carrier.

54. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 2 in combination with a pharmaceutically acceptable carrier.

55. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 12 in combination with a pharmaceutically acceptable carrier.

56. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 23 in combination with a pharmaceutically acceptable carrier.

57. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 33 in combination with a pharmaceutically acceptable carrier.

58. A method of inducing cytokine biosynthesis in an animal comprising administering a therapeutically effective amount of a compound of claim 1 to the animal.

59. A method of treating a viral disease in an animal comprising administering an effective amount of a compound of claim 1 to the animal.

60. A method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound of claim 1 to the animal.

61. A method of inducing cytokine biosynthesis in an animal comprising administering a therapeutically effective amount of a compound of claim 2 to the animal.

62. A method of treating a viral disease in an animal comprising administering an effective amount of a compound of claim 2 to the animal.

63. A method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound of claim 2 to the animal.

64. A method of inducing cytokine biosynthesis in an animal comprising administering a therapeutically effective amount of a compound of claim 12 to the animal.

65. A method of treating a viral disease in an animal comprising administering an effective amount of a compound of claim 12 to the animal.

66. A method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound of claim 12 to the animal.

67. A method of inducing cytokine biosynthesis in an animal comprising administering a therapeutically effective amount of a compound of claim 23 to the animal.

68. A method of treating a viral disease in an animal comprising administering an effective amount of a compound of claim 23 to the animal.

69. A method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound of claim 23 to the animal.

70. A method of inducing cytokine biosynthesis in an animal comprising administering a therapeutically effective amount of a compound of claim 33 to the animal.

71. A method of treating a viral disease in an animal comprising administering an effective amount of a compound of claim 33 to the animal.

72. A method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound of claim 33 to the animal.

73. A method of inducing cytokine biosynthesis in an animal comprising administering a therapeutically effective amount of a composition of claim 52 to the animal.

74. A method of treating a viral disease in an animal comprising administering an effective amount of a composition of claim 52 to the animal.

75. A method of treating a neoplastic disease in an animal comprising administering an effective amount of a composition of claim 52 to the animal.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/15656

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/4745, 31/437 ; C07D 471/02
US CL :514/293 ; 546/82
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/293 ; 546/82

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 9,208,584 A1 (NANBA et al.) 12 August 1997 (12.08.97), Compounds I, II, II' and III on page 2, column 1.	1-750
A,P	US 6,069,149 A (NANBA et al.) 30 May 2000 (30.05.00), examples 39-60 in columns 44-56.	1-75

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
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Date of the actual completion of the international search 31 JULY 2000	Date of mailing of the international search report 04 OCT 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CHANA AULAKH Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)*

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 October 2001 (11.10.2001)

PCT

(10) International Publication Number
WO 01/74343 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/US01/10291

(22) International Filing Date: 30 March 2001 (30.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/193,120 30 March 2000 (30.03.2000) US
09/820,420 29 March 2001 (29.03.2001) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/74343 A2

(54) Title: METHOD FOR THE TREATMENT OF DERMAL LESIONS CAUSED BY ENVENOMATION

(57) Abstract: A method of treating dermal lesions caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the lesion is disclosed.

Method for the Treatment of Dermal Lesions Caused by Envenomation

Field of the Invention

The present invention relates to methods for treating dermal lesions caused by envenomation. In particular the present invention relates to a method of treating dermal lesions caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the lesion.. The present invention also provides a method of preventing dermonecrosis caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the envenomation.

Background of the Invention

Many imidazoquinoline amine, imidazopyridine amine, 6,7-fused cycloalkylimidazopyridine amine, imidazonaphthyridine amine, tetrahydroimidazonaphthyridine amine, oxazolopyridine amine, oxazoloquinoline amine, thiazolopyridine amine, thiazoloquinoline amine and 1,2-bridged imidazoquinoline amine immune response modifiers are known. These compounds are hereinafter sometimes referred to as immune response modifying compounds (IRMs). Such compounds, methods for preparing them, formulations containing them and methods of using them are disclosed in, for example, U.S. Patent Nos. 4,689,338; 5,389,640; 5,268,376; 4,929,624; 5,266,575; 5,352,784; 5,494,916; 5,482,936; 5,395,937; 5,238,944; 5,175,296; 5,693,811; 5,741,908; 5,756,747; 5,939,090; 6,110,929; 4,988,815; 5,376,076; 6,083,505; 6,039,969;

and PCT Publications WO 99/29693, WO 00/40228, WO 00/76505, WO 00/76518 and WO 00/76518.

The IRM compounds have demonstrated antiviral and antitumor activity. The antiviral and antitumor activity is not direct but is believed to result from their ability to stimulate an innate immune response. In cultures of human peripheral blood mononuclear cells, members of this class of compounds have been shown to stimulate the production and release of a variety of cytokines and chemokines including interferon-α, tumor necrosis factor-α, interleukin-1 (IL-1), IL-1 receptor antagonist, IL-6, IL-8, IL-12, monocyte chemotactic protein-1 (MCP-1) and macrophage inflammatory protein (MIP-1α).

In addition to stimulating an innate immune response, the IRM compounds have been found to mediate the acquired immune response. In human peripheral blood mononuclear cell cultures, members of this class of compounds have been shown to induce the production of the T helper type 1 (TH1) cytokine interferon-γ and to inhibit the production of T helper type 2 (TH2) cytokines IL-4 and IL-5.

One of these IRM compounds, known as imiquimod (1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine), has been commercialized in a topical formulation, Aldara™ cream, for the treatment of anogenital warts associated with human papillomavirus. Imiquimod is also being evaluated in clinical trials for use in treating superficial basal cell carcinoma and actinic keratosis.

Another of these IRM compounds, known as resiquimod (4-amino-2-ethoxymethyl-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol), is being evaluated in clinical trials for use in preventing genital herpes recurrences.

There are numerous venomous flora and fauna in the world, some of which possess venom that causes significant medical problems when a human or an animal is exposed to the venom. Envenomation by such a plant or animal can cause both systemic and local reactions. Examples of local reactions include edema, erythema, induration, necrotic ulcers, pain, pruritis, and vesicles. The severity of the reaction is dependent on a variety of factors including the source of the venom (e.g. *Loxosceles* spider, box jellyfish, fire ant), the amount of venom injected, the location of the bite or sting (e.g. arm, thigh), and prior exposure to the venom. A variety of treatments have been used including analgesics, antibiotics, antivenoms, corticosteroids, Dapsone, and hyperbaric oxygen. In those

instances where the initial dermal lesion progresses to dermonecrosis, surgical intervention is often necessary. There is a continuing need for new treatments and in particular for treatments that will prevent dermonecrosis.

Summary of the Invention

The present invention relates to a method of treating dermal lesions caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the lesion.

The present invention also provides a method of preventing dermonecrosis caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the envenomation.

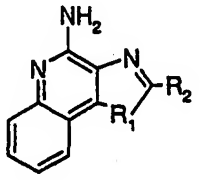
Detailed Description of the Invention

As used herein the term "envenomation" means injection of a poisonous material (venom) by sting, spine, fang, tooth, or other venom delivery apparatus.

Immune response modifier (IRM) compounds that are useful in practicing the methods of the present invention are selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines. Such compounds and methods for preparing them are disclosed in, for example, U.S. Patent Nos. 4,689,338; 5,389,640; 5,268,376; 4,929,624; 5,266,575; 5,352,784; 5,494,916; 5,482,936; 5,395,937; 5,175,296; 5,693,811; 5,741,908; 5, 756,747; 6,110,929; 4,988,815; 5,376,076; 6,083,505;

6,039,969; and International Publications WO 99/29693; WO 00/76505; WO 00/76518 and WO 00/76518. The entire disclosure of each of these patents and patent applications is incorporated herein by reference.

Preferred IRM compounds for use in the practice of the methods of the invention include compounds of Formula I



I

wherein

R_1 is selected from the group consisting of S and NR_3,

R_2 is selected from the group consisting of hydrogen, straight and branched chain alkyl containing one to six carbon atoms, and alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms; and

R_3 is selected from the group consisting of straight and branched chain alkyl containing one to six carbon atoms and straight and branched chain hydroxy alkyl containing one to six carbon atoms; or a pharmaceutically acceptable salt thereof.

Preferred R_2 groups include hydrogen, methyl, ethyl, propyl, butyl, and ethoxymethyl.

Preferred R_3 groups include 2-methylpropyl and 2-hydroxy-2-methylpropyl.

Particularly preferred IRM compounds include 4-amino-2-ethoxymethyl-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol (resiquimod), 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (imiquimod), 2-methylthiazolo[4,5-*c*]quinolin-4-amine, 2-ethylthiazolo[4,5-*c*]quinolin-4-amine, 2-propylthiazolo[4,5-*c*]quinolin-4-amine and 2-butylthiazolo[4,5-*c*]quinolin-4-amine.

In the method of the invention a therapeutically effective amount of the IRM compound is applied. The term "therapeutically effective amount" means an amount sufficient to induce a therapeutic effect such as the amelioration of symptoms (e.g. pain, erythema diminution of lesions,) or the prevention of dermonecrosis. The specific amount

that will constitute a therapeutically effective amount will vary according to factors readily determined by those skilled in the art including the activity of the particular IRM compound being used, the particular formulation being administered, the duration of the administration and the frequency of the administration. Generally from about 1 μg to about 125 mg, preferably from about 10 μg to about 25 mg, of the IRM compound is applied to the dermal lesion.

Any conventional dosage form suitable for topical application may be used including creams, gels, lotions, ointments, sprays and transdermal patches. Preferred formulations include creams and gels. Suitable formulations are disclosed, for example, in U.S. Patents 5,238,944 and 5,939,090 and International Publication WO 00/40228, the disclosures of which are incorporated by reference herein.

The frequency and duration of administration can vary as needed for amelioration of symptoms and/or prevention of dermonecrosis. Treatment regimens may include administration from twice per day to once per week, preferably two to three times per week, for at least one week, preferably for two to three weeks.

There are many venomous creatures whose bite or sting causes local reactions in humans. Examples of such creatures include, for example, arthropods such as arachnids (e.g., scorpions, spiders) and insects of the order Hymenoptera (e.g., bees, wasps, ants), and marine animals such as jellyfish, stone fish, stingrays, and blue ringed octopus. The venom of some species is known to cause dermal lesions that can progress to dermonecrosis. Examples of such species include *Loxosceles* spiders (*L. reclusa, L. deserta, L. laeta*), hobo spiders (*Tegenaria* spp), yellow sac spiders (*Cheiracanthium* spp.), fire ants (*Solenopsis invicta*), and jellyfish (*Chironex fleckeri, Carybdea alata, Cassiopea andromeda, Aurelia aurita*).

Venoms are frequently complex mixtures of a variety of substances. Substances that have been identified include enzymes e.g. phospholipases, hyaluronidases, cholinesterases; alkaloids e.g. methyl-N-piperidine; proteins e.g. melittin; and peptides. The particular constituents will depend on the source of the venom. When envenomation occurs a number of different types of epithelial and endothelial cells are exposed to the venom. These cells are capable of synthesizing and releasing a wide variety of chemokines and cytokines in response to a variety of stimuli. For example, it has been shown *in vitro* that *Loxosceles deserta* venom induces endothelial and epithelial cells to

secrete both α and β chemokines. The release of chemokines and cytokines triggers additional events such as the attraction of neutrophils to the site of envenomation. While some of the local skin reactions that are manifested as a result of envenomation such as edema and erythema are caused directly by constituents of the venom due to the hemolytic action of various enzymes, it has been hypothesized that dermonecrosis may be due to an immune response.

While not wishing to be bound by theory, it is believed that effects of the IRM compound overwhelm the local physiological effects of the venom. This may occur by modifying the qualitative properties of the local soluble mediators of inflammation such that signaling for neutrophil activation and degranulation is inhibited. In addition, the early aggregation of neutrophils in dermal blood vessels may be diffused by IRM compound induced cytokines by stimulating the migration of neutrophils out of local vasculature and into surrounding tissue. Thus, if activated neutrophils are no longer aggregated in the discrete focal area of the site of envenomation, the amount of central necrosis may be inhibited. In essence, the venom induced "immune dysregulation" may be overcome by the immune stimulation provided by the IRM compound.

Example

Treatment of *Loxosceles reclusa* envenomation with Imiquimod 5% Cream

Background

A privatized correctional facility in Texas experienced a cluster of spider bite cases due to *L. reclusa* shortly following the receipt of a shipment of used mattresses from a local county jail. Spiders may have inhabited the mattresses when they were stored for several weeks in a dark shed out behind the facility. Following the first several cases, fumigation with a synthetic pyrethroid (PT 1200, resmethrin) was performed. While this agent is considered effective against *L. reclusa*, the spiders must generally be contacted directly, and unhatched eggs are less susceptible.

The diagnosis of loxoscelism in these cases was made by exclusion. No spiders were recovered despite the use of glue traps, although in one case, a "brown spider" dropped from the ceiling of a shower onto the breast of a female patient, who brushed the spider away after sustaining a bite. The following aspects of these cases favor a diagnosis

of *L. reclusa* envenomation: the spider is endemic to the area; the bites occurred mostly at night and were characterized by lack of immediate pain. Blanching and cyanosis slowly developed at the central core, with spreading erythema and progression to dermonecrosis. Other insects are known to inflict bites with similar clinical findings but can be excluded on the grounds that they are not found in Texas (various tarantulas, Australian funnel-web spiders (*Atrax spp.*), "hobo spiders" (*Tegeneria spp.*); they form characteristic webs not found in the facility (yellow sac spiders (*Chiracanthium spp.*), black-and-yellow orb weavers (*Argiope spp.*); or they bite during the day ("jumping spider" (*Phidippus audax*)). *Phidippus* species are very aggressive and bite commonly, but they inflict only slightly painful bites resulting in erythematous papules or small urticarial wheals. The only alternative suspect is *Latrodectus mactans* ("Southern black widow"). This spider is shy in behavior, similar to *L. reclusa*, and bites often go unnoticed until a red papule progresses to a larger halo or target lesion up to 2 cm in diameter. Unlike the *L. reclusa* bite however, skin manifestations are minimal. Victims are more likely to experience muscle spasms and cramping within hours of envenomation, together with weakness of the legs and tightness of the chest. These clinical findings were absent in the cases reported here.

Methods

Patients were seen in the facility clinic on the day they complained of a painful lesion. Most patients related a history of discovering the lesion upon awakening in the morning. The treatment of the first 12 consecutive cases, occurring over a 5 month period, consisted of a single intramuscular dose of ceftriaxone 1 gm and oral dicloxicillin 500 mg bid x 10 days, plus either topical triamcinolone 0.1% applied bid, topical papain-urea-chlorophyllin copper complex sodium debriding-healing ointment (Panafil™) applied daily, or daily topical becaplermin (rh-PDGF-BB) 0.01% gel (Regranex™). Where necessary and appropriate, patients were transported to the local University Medical Center for surgical debridement of necrotic lesions.

A consecutive series of 7 bites on 5 patients were treated with imiquimod 5% cream (available under the tradename ALDARA from 3M Pharmaceuticals, St. Paul, MN, USA) applied by the clinic staff, three times per week (typically Monday, Wednesday and Friday) for two weeks. Sufficient cream was used to cover the area of erythema, rubbing

the cream gently until it "vanished" as per labeled instructions. In addition, a single intramuscular dose of ceftriaxone 1 gm was given together with oral dicloxicillin, 500 mg bid for 10 days. Patients were re-examined by a physician at 7, 14 and 28 days following initiation of therapy.

Results

The first 12 patients, managed using conventional therapy, presented with tender to painful lesions consisting of a central core of induration and blanching, surrounded by 3-8 cm of erythema. Among these, 7 progressed to tissue necrosis within 1 week after the bite, all of whom were referred for surgical debridement. One patient developed a healing contracture of the forearm which necessitated surgical release. Healing occurred by secondary intention over several months following the bites.

Seven consecutive bites occurring in 5 patients were treated with imiquimod. These cases are summarized in the Table below. Presenting signs and symptoms were consistent with those recorded for patients treated by conventional means. Tenderness or pain, with erythema, characteristic blanching and firm induration were present in every case. In one case (L.S.), punctuate marks were noted at the center of the indurated area. Pain relief was reported by all patients within 1-2 days following the first dose of imiquimod. Marked improvement in both induration and erythema was noted by day 7, with full resolution in all but one case by day 14. In patient Y.C., erythema was noted to be cleared at the day 7 visit but developed again by day 14. The reappearance of erythema is presumed to be secondary to imiquimod

Patients C.R. and L.S. each sustained two bites. In the case of L.S., the first bite was resolved 9 days after it occurred. The second bite occurred 16 days after the first bite and resolved completely, with treatment, by the 5th day. The difference in clinical course may have been due to differences in the age of the spider, the sex of the spider (females inject greater volumes of venom), or an acquired immunity following the first bite. Necrosis did not develop in any of the imiquimod treated cases. No residual scarring or pigmentation changes were noted at the day 28 follow-up visit.

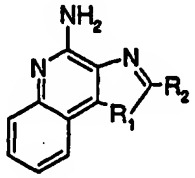
The probability of observing 0 out of 7 consecutive cases with no necrosis, given the underlying historical rate of 7/12 (0.583), is quite low based on a binomial probability distribution ($p=0.002$) or a Chi-square analysis ($p=0.01$).

Summary of Cases				
Patient/Age/Sex	Bite Location	Presentation	7 Day Follow-up	14 Day Follow-up
R.M/ 39y/ M	Right calf	1.5 cm induration 9 cm erythema Painful	0.5 cm induration No erythema No pain or tenderness	Completely healed
R.H/ 45y/ M	Right calf	1.3 cm induration 10 cm erythema Very painful	1.25 cm firm induration 5 cm induration Non-tender	Completely healed
L.S./ 28y/ F	Right thigh	1.5 cm induration 7.5 x 11 cm erythema Tender	2.5 cm central core No erythema No pain or tenderness	Completely healed
L.S./ 28y/ F	Left buttock	1.0 cm induration Erythema Painful	Completely healed	
C.R./ 35y/ F	Left thigh	1.0 cm central core 6.0 cm erythema Painful	0.5 cm central core 2.0 cm erythema	Completely healed
C.R./ 35y/ F	Right breast	1.2 cm central core 3.0 cm erythema Painful	1.0 cm central core No erythema	Completely healed
Y.C./ 35y/ F	Right calf	1.8 cm central core 1.2 cm erythema Painful	0.75 cm ulcer No erythema Decreased pain	Ulcer healed Erythema present (Erythema resolved by d28)

WHAT IS CLAIMED IS:

1. A method of treating dermal lesions caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the lesion.

2. The method of Claim 1 wherein the immune response modifier compound is a compound of Formula I



I

wherein

R_1 is selected from the group consisting of S and NR_3,

R_2 is selected from the group consisting of hydrogen, straight and branched chain alkyl containing one to six carbon atoms, and alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms; and

R_3 is selected from the group consisting of straight and branched chain alkyl containing one to six carbon atoms and straight or branched chain hydroxy alkyl containing one to six carbon atoms; or a pharmaceutically acceptable salt thereof.

3. The method of Claim 2 wherein R_1 is NR_3.

4. The method of Claim 2 wherein R_1 is S.

5. The method of Claim 2 wherein R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, and ethoxymethyl.

6. The method of Claim 2 wherein R_3 is selected from the group consisting of 2-methylpropyl and 2-hydroxy-2-methylpropyl.

7. The method of Claim 2 wherein the IRM compound is selected from the group consisting of 4-amino-2-ethoxymethyl-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol, 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine, 2-methylthiazolo[4,5-*c*]quinolin-4-amine, 2-ethylthiazolo[4,5-*c*]quinolin-4-amine, 2-propylthiazolo[4,5-*c*]quinolin-4-amine and 2-butylthiazolo[4,5-*c*]quinolin-4-amine.

8. The method of Claim 1 wherein the immune response modifier compound is applied via a cream or a gel.

9. The method of Claim 1 wherein the source of the envenomation is an arthopod.

10. The method Claim 9 wherein the arthopod is a spider.

11. The method of Claim 9 wherein the arthodpod is an insect of the order Hymenoptera.

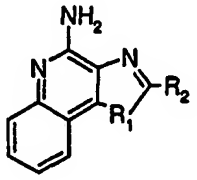
12. The method of Claim 1 wherein the source of envenomation is a marine animal.

13. The method of Claim 12 wherein the marine animal is a jellyfish.

14. A method of preventing dermonecrosis caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline

amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the envenomation.

15. The method of Claim 14 wherein the immune response modifier compound is a compound of Formula I



I

wherein

R_1 is selected from the group consisting of S and NR_3,

R_2 is selected from the group consisting of hydrogen, straight and branched chain alkyl containing one to six carbon atoms, and alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms; and

R_3 is selected from the group consisting of straight and branched chain alkyl containing one to six carbon atoms and straight or branched chain hydroxy alkyl containing one to six carbon atoms; or a pharmaceutically acceptable salt thereof.

16. The method of Claim 15 wherein R_1 is NR_3.

17. The method of Claim 15 wherein R_1 is S.

18. The method of Claim 15 wherein R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, and ethoxymethyl.

19. The method of Claim 15 wherein R_3 is selected from the group consisting of 2-methylpropyl and 2-hydroxy-2-methylpropyl.

20. The method of Claim 15 wherein the IRM compound is selected from the group consisting of 4-amino-2-ethoxymethyl-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-

ethanol, 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine, 2-methylthiazolo[4,5-*c*]quinolin-4-amine, 2-ethylthiazolo[4,5-*c*]quinolin-4-amine, 2-propylthiazolo[4,5-*c*]quinolin-4-amine and 2-butylthiazolo[4,5-*c*]quinolin-4-amine.

21. The method of Claim 14 wherein the immune response modifier compound is applied via a cream or a gel.

22. The method of Claim 14 wherein the source of the envenomation is an arthopod.

23. The method Claim 22 wherein the arthopod is a spider.

24. The method of Claim 22 wherein the arthodpod is an insect of the order Hymenoptera.

25. The method of Claim 14 wherein the source of envenomation is a marine animal.

26. The method of Claim 25 wherein the marine animal is a jellyfish.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 October 2001 (11.10.2001)

PCT

(10) International Publication Number
WO 01/74343 A3

(51) International Patent Classification[7]: A61K 31/4745, 31/429

(21) International Application Number: PCT/US01/10291

(22) International Filing Date: 30 March 2001 (30.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/193,120	30 March 2000 (30.03.2000)	US
09/820,420	29 March 2001 (29.03.2001)	US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
7 February 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/74343 A3

(54) Title: METHOD FOR THE TREATMENT OF DERMAL LESIONS CAUSED BY ENVENOMATION

(57) Abstract: A method of treating dermal lesions caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the lesion is disclosed.

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/US 01/10291

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4745 A61K31/429

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, PAJ, BIOSIS, MEDLINE, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 20847 A (MINNESOTA MINING AND MANUFACTURING COMPANY) 28 October 1993 (1993-10-28) cited in the application the whole document	2-7, 15-20
A	WO 00 06577 A (3M INNOVATIVE PROPERTIES CO.) 10 February 2000 (2000-02-10) cited in the application the whole document	2-7, 15-20
A	US 5 389 640 A (MINNESOTA MINING AND MANUFACTURING COMPANY) 14 February 1995 (1995-02-14) cited in the application the whole document	2-7, 15-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 October 2001	31/10/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Economou, D

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Form PCT/ISA/210 (second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,8-14,21-26

Present claims 1,8-14,21-26 relate to an extremely large number of possible compounds/methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds/methods disclosed in claims 2-7 and 15-20.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

ormation on patent family members

Inter onal Application No
PCT/US 01/10291

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(12)特許協力条約に基づいて公開された国際出願

(19) 世界知的所有権機関
国際事務局

(43) 国際公開日
2002年5月10日 (10.05.2002)

PCT

(10) 国際公開番号
WO 02/36592 A1

(51) 国際特許分類7: C07D 471/04, A61K 31/4745, A61P 17/00, 17/02, 17/06, 35/00

(21) 国際出願番号: PCT/JP01/09575

(22) 国際出願日: 2001年10月31日 (31.10.2001)

(25) 国際出願の言語: 日本語

(26) 国際公開の言語: 日本語

(30) 優先権データ:
特願2000-337359 2000年11月6日 (06.11.2000) JP

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(81) 指定国 (国内): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) 指定国 (広域): ARIPO 特許 (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI 特許 (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[続葉有]

(54) Title: REMEDIES FOR ARACHIDONIC ACID-INDUCED SKIN DISEASES

(54) 発明の名称: アラキドン酸誘発皮膚疾患治療剤

(57) Abstract: Drugs for preventing and/or treating arachidonic acid-induced skin diseases which contain as the active ingredient 4-amino-2-ethoxymethyl-α,α dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol:R848 or its acid addition salt or solvate. By using these drugs, various skin diseases caused by the accelerated arachidonic acid metabolism (psoriasis, ultraviolet dermatitis, mastocytoma, basiloma, squamous cell carcinoma, etc.) can be safely and effectively treated.

(57) 要約:

４－アミノ－２－エトキシメチル－α，αジメチル－１Ｈ－イミダゾ［４，５－ｃ］キノリン－１－エタノール：Ｒ８４８、又はその酸付加塩若しくは溶媒和物を有効成分とする、アラキドン酸代謝亢進に起因する皮膚疾患の予防及び／又は治療のための薬剤。これにより、アラキドン酸代謝亢進に起因する各種皮膚疾患（乾癬、紫外線皮膚炎、肥満細胞症及び基底細胞腫、有刺細胞癌等）を安全かつ効果的に治療できる。

WO 02/36592 A1

添付公開書類:
— 国際調査報告書

2文字コード及び他の略語については、定期発行される各PCTガゼットの巻頭に掲載されている「コードと略語のガイダンスノート」を参照。

明細書

アラキドン酸誘発皮膚疾患治療剤

技術分野

本発明は、皮膚疾患治療剤に関する。さらに詳しくは、乾癬、紫外線皮膚炎、肥満細胞症、基底細胞癌または有刺細胞癌などのアラキドン酸代謝亢進に起因する皮膚疾患の予防または治療剤に関する。

背景技術

アラキドン酸代謝経路により生成されるプロスタグランジン（ＰＧ）類やロイコトリエン類(ＬＴ)は、胃酸分泌や血小板凝集、種々の平滑筋収縮など生理的機能調節に係わるとともに組織の炎症を惹起する脂肪酸系の情報伝達物質（メディエーター）である。ＰＧやＬＴは生体の恒常性維持に重要であるが、一部の皮膚疾患においては、その過剰産生が疾患の主たる病因と考えられている。

このような皮膚疾患の代表例として、まず乾癬が挙げられる。乾癬は表皮細胞の良性の異常増殖と、表皮内への多形核白血球の侵入を示す慢性疾患であり、下記(1)～(4)の理由から、アラキドン酸代謝産物異常と密接に関連する疾患と考えられている。(1)乾癬皮疹部ではＰＧ、アラキドン酸、１２－ＨＥＴＥが増加する (Hammerstrom, S. et al. Proc. Nat. Acad. Sci. USA. 72, 5130-5134 (1975))、(2)ＬＴＢ４をヒト皮膚に貼布すると、乾癬皮疹部にみられる表皮内の微小膿瘍が形成される(Camp, S. et al. J. Invest. Dermatol. 82, 202-204 (1984))、(3)ＰＧの血管拡張作用とロイコトリエンＣ、ＤおよびＥ(ＬＴＣ、ＬＴＤ、ＬＴＥ)の血管透過性亢進により皮膚の発赤・浮腫反応が惹起される、(4)ロイコトリエン５，１２－ジヒドロキシ体(ＬＴＢ４)により多核白血球遊走が増強され乾癬等に特徴的な角層下、角層内膿ほうが形成される。現在、トレチナート(ビタミンＡ誘導体)、活性

型ビタミンＤ３、シクロスポリンなどが用いられているが、副作用などの面でより有用な乾癬治療剤が望まれている(皮膚疾患最新の治療 '９７－'９８、ｐ４－７、１０６－１０７)。

アラキドン酸代謝異常に起因する皮膚疾患の代表例として、他に下記の疾患が挙げられる。

肥満細胞症： 皮膚で増殖した肥満細胞からヒスタミンなどが放出され、皮膚の潮紅と蕁麻疹を呈する症状である。これらの症状は主としてヒスタミンによると考えられているため抗ヒスタミン薬が使用されるが、ＰＧ合成阻害剤を投与すると著明な改善が見られるヒスタミン抵抗性の症例(Main, R. A. et al. Br. J. Dermatol.107(Suppl. 22), 53 (1982))やＰＧＤ２の過剰産生が知られている(Roberts, L. J. et al. N. Engl. J. Med.303, 1400-1404 (1980))。

日光皮膚炎：中波長紫外線によりＰＧなどの炎症性メディエーターが血管拡張を惹起すると考えられている。

基底細胞癌あるいは有刺細胞癌（いずれも皮膚癌）：ＰＧが増加しており、その腫瘍の増殖にＰＧが関与する事が示唆されている(Vanderveen, E. E. et al. Arch.Dermatol. 122, 407-412(1986))。

一方、4-アミノ-2-エトキシメチル-α,α-ジメチル-１Ｈ－イミダゾ[4,５－ｃ]キノリン－１－エタノール（Ｒ８４８）は、 下記の薬理作用が知られている化合物である。

1)抗ウイルス作用：ヘルペスウィルス(Tomai. MA. et al. Antiviral Res. 28, 253-264(1995))感染系での抗ウィルス作用が報告されている。

2）サイトカイン誘導作用： ＩＦＮ、インターロイキン類(ＩＬ－１、ＩＬ－６、ＩＬ－８)や腫瘍壊死因子α(ＴＮＦ－α)の産生を誘導することが報告されている(Wagner et al. Cytokine 9 837-845 (1997))。

Ｒ８４８と 1-(2-メチルプロピル)－1H-イミダゾ[4,5-c]キノリン-4-アミン（イミキモド）について、Ｔｈ２型サイトカイン産生阻害作用を利用したアレルギー性

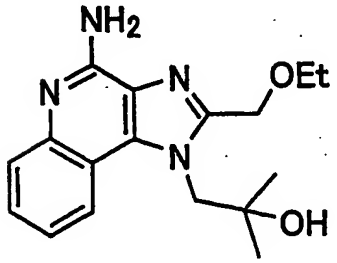
皮膚炎への医薬適用については公知である（WO 98/17279）。また、イミキモドについては、アラキドン酸代謝異常に起因する皮膚疾患への適用が本発明者らにより特許出願されている（特開 2000-247884）。しかし、Ｒ８４８がアラキドン酸代謝異常に起因する皮膚疾患に何らかの予防／治療効果を示すことに関して、上述の先行技術文献は何も記載していない。むしろ、イミキモドに無く、Ｒ８４８にのみ認められるＴＮＦ－αの産生誘導作用（Wagner et al. Cytokine 9 837-845 (1997)）は、ＴＮＦ－αの皮膚炎症惹起作用（Kondo, S et al. Eur. J. Immunol. 27, 1713-8(1997)）と相まって、Ｒ８４８の皮膚炎症惹起の可能性を示唆するものである。

発明の開示

本発明の課題は、アラキドン酸代謝亢進に起因する皮膚疾患、即ち、ＰＧ、ＬＴ等の産生亢進に起因する皮膚疾患を治療および／または予防するための新規な皮膚疾患治療剤の提供である。

本発明者らは、すでにイミキモドのアラキドン酸誘発マウス耳浮腫抑制作用を見いだし、乾癬などの皮膚疾患治療剤の発明として特許出願している（特開 2000-247884、前出）。しかし、今回、イミキモドの類縁化合物Ｒ８４８が極めて強く持続性のあるアラキドン酸誘発マウス耳浮腫抑制作用を示すことを発見し、本発明を完成した。すなわち本発明の要旨は、以下の［1］～［6］で表される。

［1］ 下式で表される化合物



（4-アミノ-2-エトキシメチル-α,α-ジメチル-１Ｈ－イミダゾ[4,5－c]キノリン－１－エタノール、以下、Ｒ８４８と略す）またはその酸付加塩または溶媒和物

を有効成分とするアラキドン酸代謝亢進に起因する皮膚疾患の予防および／または治療のための薬剤。

［2］ アラキドン酸代謝亢進に起因する皮膚疾患が乾癬、紫外線皮膚炎、肥満細胞症、基底細胞癌または有刺細胞癌である［1］記載の薬剤。

［3］ 経口投与用剤形である［1］または［2］に記載の薬剤。

［4］ 約０．１～約１０００ｍｇ／日の投与単位用量のＲ８４８を含有する［3］記載の薬剤。

［5］ 非経口投与用剤形である［1］または［2］に記載の薬剤。

［6］約０．１～約５０ｍｇ／日の投与単位用量のＲ８４８を含有する外用剤である［5］記載の薬剤。

本発明において、「アラキドン酸代謝昂進に起因する皮膚疾患」とは、アラキドン酸代謝経路（アラキドン酸カスケード）を構成するアラキドン酸およびその代謝物の異常な増加によって生じる皮膚疾患を意味し、具体的疾患名としては、乾癬、紫外線皮膚炎、肥満細胞症、基底細胞癌または有刺細胞癌が挙げられる。アラキドン酸代謝物とは、（１）シクロオキシゲナーゼ酵素により産生されるプロスタグランジン類：ＰＧＥ（プロスタグランジンＥ）、ＰＧＦ、ＰＧＩ、ＴＸＡ（トロンボキサンＡ）など、（２）リポキシゲナーゼ酵素により産生されるロイコトリエン類： ＬＴＢ４、ＬＴＣ、ＬＴＤ、ＬＴＥ等、および（３）１２－ＨＥＴＥ等を意味し、これらのメディエーターが異常に増加した結果生じる炎症性の皮膚疾患が、本発明の適用対象である。

ただし、本発明における皮膚疾患には、ウィルスや細菌感染症、火傷凍傷、外傷による皮膚炎症、膠原病（全身性エリテマトーデス、強皮症などの自己免疫疾患）に伴う皮膚疾患、異種免疫反応によって生じるアレルギー性皮膚疾患（蕁麻疹、接触皮膚炎、アトピー性皮膚炎など）は含まれない。

以下に本発明の有効成分とその製造方法について述べる。

本発明の有効成分であるＲ８４８およびその酸付加塩は、公知の方法に準じて容易に合成することができる。例えば、WO98/17279 に記載の方法に準じればよい。Ｒ８４８の酸付加塩の酸としては、薬理学的に許容される酸であれば特に限定されず、水和物等の溶媒和物であってもよい。酸付加塩は、無機酸（例えば、塩酸、臭化水素酸、硫酸、リン酸および硝酸等）や酢酸、蓚酸、酒石酸、コハク酸、リンゴ酸、アスコルビン酸、安息香酸、タンニン酸、パモイン酸、アルギニン酸、ポリグルタミン酸、ナフタレンスルホン酸、ナフタレンジスルホン酸およびポリガラクトゥロン酸(polygalacturonic acid)のような有機酸とで形成される。塩酸、硫酸、酢酸、蓚酸、アスコルビン酸などが好適な酸付加塩である。

Ｒ８４８およびその塩は、種々の製剤形態（例えば、液剤、固形剤、カプセル剤等）をとりうる。経口投与のための剤型としては、例えば、錠剤、カプセル剤、丸剤、顆粒剤、散剤、液剤、懸濁剤などが挙げられ、非経口投与のための剤型としては、例えば、注射用水性剤、もしくは油性剤、軟膏剤、クリーム剤、ローション剤、エアロゾル剤、坐剤、貼付剤などが挙げられる。

また、所望の作用を損なわない他の活性材料、または抗生物質、抗真菌剤、他の抗炎症剤または抗ウイルス性化合物のような所望の作用を補足する材料と混合して用いることもできる。

経口治療投与の目的のために、活性成分は賦形剤に組み込み、液剤、粉剤、散剤、錠剤、トローチまたはカプセルで用いることができる。薬学的に相溶性のある結合剤および／またはアジュバント材料を組成物の一部として含むことができる。錠剤、丸剤、カプセルおよびトローチ等は、任意の、以下の性質が類似している成分または化合物を含むことができる：微結晶性セルロース、ガムトラガカントまたはゼラチンのような結合剤；澱粉またはラクトースのような賦形剤；アルギン酸、リモゲル（rimogel）またはコーンスターチのような分散剤；ステアリン酸マグネシムまた

はステローツ（Sterotes）のような潤滑剤；コロイド状二酸化ケイ素のような滑剤；スクロースまたはサッカリンのような甘味料；または、ペッパーミント、サリチル酸メチルまたはオレンジ風味剤のような風味剤。投与単位形態がカプセルの場合、前述の種類の材料に加えて、脂肪油のような液体キャリヤーを含むことができる。さらに、投与単位形態は、投与単位の物理的形態を改良する種々の他の材料、例えば糖の被膜、シェラックまたは溶腸性剤を含むことができる。Ｒ８４８および薬学的に許容できる塩は、エリキシル、懸濁液、シロップ、ウエハース、またはチューインガム等の成分として投与することができる。シロップは、活性成分に加えて、甘味料としてのスクロース、および特定の防腐剤、染料および着色剤ならびに風味料を含み得る。

また、Ｒ８４８は、移植およびマイクロカプセル投与系を含む徐放性製剤として調製されうる。担体としては、エチレン酢酸ビニル、ポリ無水物、ポリグリコール酸、コラーゲン、シリコン、ポリオルトエステルおよびポリ乳酸のような生分解性で生物適合性のポリマーを用いることができる。そのような製剤を調製する方法は当業者に明らかであり、材料も市販品として入手できる。　また、リポソーム懸濁液も適当な脂質（例えばステアロイルホスファチジルエタノールアミン、ステアロイルホスファチジルコリン、アラカドイルホスファチジルコリンおよびコレステロール）を担体に用いて当業者に知られている方法によって調製することができる。

Ｒ８４８を有効成分として含有する非経口、皮内、皮下または局所適用のために用いられる溶液または懸濁液は以下の成分を含むことができる。注入用水、塩水溶液、固定油(fixedoil)、　ポリエチレングリコール、グリセリン、プロピレングリコールまたは他の合成溶媒のような滅菌希釈剤；ベンジルアルコールまたはメチルパラベンのような殺菌剤；アスコルビン酸または亜硫酸水素ナトリウムのような酸化防止剤；エチレンジアミン四酢酸のようなキレート化剤；アセテート、クエン酸

またはリン酸のような緩衝剤および塩化ナトリウムまたはデキストロースのような張度を調整するための薬剤など。非経口製剤は、アンプル、使い捨て注射器またはガラスまたはプラスチック製の複投与量バイアル中に封入し得る。注射剤は、常法により調製することができ、例えば、当該化合物を適切な溶剤（例えば、滅菌された水、緩衝液、生理食塩水等）に溶解した後、フィルター等で濾過して滅菌し、次いで無菌的な容器に充填することにより調製することができる。静脈内に投与する場合、好ましいキャリヤーは生理食塩水またはリン酸緩衝食塩水(PBS)である。

本発明において、外用剤は特に好適な剤型の一つである。Ｒ８４８は、近似の化学構造を有するイミキモド、1-(2-メチルプロピル)－1H-イミダゾ[4,5-c]キノリン-4-アミンと比較した場合、少なくとも２０倍水溶性が高いという特性を持つ（ｐＨ 2.5、5.5,および７での水溶解度 1000μｇ/ml 以上）。この特性により、本発明の医薬は製剤化が容易なだけでなく、中枢や他の組織への有効成分移行性が低い。また、患部での効果は持続的である。このように本発明のＲ８４８含有製剤は、外用剤として特に優れた性質を有する。

外用剤の剤型は、特に限定されるものではなく、クリーム状、ペースト状、ジェリー状、ゲル状、乳液状、液状等の形状になされたもの（軟膏剤、リニメント剤、ローション剤等）が薬物及び経皮吸収促進剤を溶解または混合分散させたものを支持体上に展延したもの（パップ剤等）、粘着剤中に上記薬物及び経皮吸収促進剤（本発明３の場合使用）を溶解または混合分散させたものを支持体上に展延したもの（プラスター剤、テープ剤等）などが挙げられる。上記基剤としては、薬学的に許容しうるものであればよく、軟膏剤、リニメント剤、ローション等の基剤として従来公知のものを用いることができ、例えば、アルギン酸ナトリウム、ゼラチン、コーンスターチ、トラガントガム、メチルセルロース、ヒドロキシエチルセルロース、カルボキシメチルセルロース、キサンタンガム、デキストリン、カルボキシメチル

デンプン、ポリビニルアルコール、ポリアクリル酸ナトリウム、メトキシエチレン－無水マレイン酸共重合体、ポリビニルエーテル、ポリビニルピロリドン等のポリマー；ミツロウ、オリーブ油、カカオ油、ゴマ油、ダイズ油、ツバキ油、ラッカセイ油、牛油、豚油、ラノリン等の油脂類；白色ワセリン、黄色ワセリン；パラフィン；ハイドロカーボンゲル軟膏（例えば、商品名プラスチベース、大正製薬社製）；ステアリン酸等の高級脂肪酸；セチルアルコール、ステアリルアルコール等の高級アルコール；ポリエチレングリコール；水などが挙げられる。さらに必要に応じて、カオリン、ベントナイト、酸化亜鉛、酸化チタン等の無機充填剤；粘度調節剤；老化防止剤；ｐＨ調節剤；グリセリン、プロピレングリコール等の保湿剤などを添加してもよい。

外用基剤（軟膏、クリームなど）の場合、一般に膏体１ｇあたり、１～１０００ｍｇの、好ましくは 3～3００mg のＲ８４８あるいはその塩を有効成分として含有させることができる。

本発明の医薬は、投与形態や投与量には特に限定は無く、適宜当業者が用いうる方法で有れば良いが、下記の方法が例示される。

すなわち、経口投与の場合、吸入剤またはカプセル剤、錠剤、顆粒剤などの剤形で投与することができ、一般に、経口投与の場合、大人では１日当たり約１～約１０００ｍｇの範囲、好ましくは約１０～約５００ｍｇの範囲を 1 回または数回に分けて投与する。

非経口投与の場合、水溶性懸濁液による皮下あるいは静脈注射剤、点滴剤、あるいは軟膏などの剤形で用いることができる。注射剤の場合、投与量は、患者の症状、年齢、体重等により異なり、また、対象疾患を有効に治療するに充分な量を適宜使用することになるが、約０．１～約５００ｍｇの範囲、好ましくは約３～約１００ｍｇの範囲を１回または数回に分けて投与することができる。外用経皮製剤（液剤、油性軟膏、親水性軟膏あるいはクリーム）の場合、使用量は、疾患の種類や症状の

程度、患部の大きさ等によって異なるが、外用剤の量として、１日当たり０．１～１００ｇ、さらに好ましくは、１～１０ｇを１回又は適当な回数に分けて患部に適用すればよい。

産業上の利用可能性

本発明により、アラキドン酸代謝異常に起因する各種皮膚疾患（乾癬、紫外線皮膚炎、肥満細胞症、基底細胞腫、有刺細胞癌等）が安全かつ効果的に治療できる。

実施例

以下、実施例を挙げて本発明を更に詳細に説明するが、本発明はこれらの実施例になんら限定されるものではない。

製剤例１　注射用液剤

精製水（２mL）に、Ｒ８４８（２００mg）およびエリスリトール（２５０mg）を溶解し、非経口投与用液剤を調製する。

製剤例２　経口用液剤

精製水（１mL）に、Ｒ８４８（２００mg）、グリセリン（２００mg）、クエン酸（６mg）およびクエン酸ナトリウム（２０mg）を溶解し、経口投与用液剤を調製する。

製剤例３　クリーム

Ｒ８４８（２ｇ）にクロタミトン５ｇ、ニッコール（ＴＳ－１０）５ｇ、流動パラフィン３ｇ、ミリスチン酸イソプロピル１５ｇを加え、７０℃に加温して溶解する。これにカルボキシビニルポリマー１ｇを水６０ｇに膨潤した溶液を加え、撹拌して乳化する。次に、ジイソプロパノールアミン０．５ｇを水９．７５ｇに溶か

した溶液を加え、均一になるまで撹拌してＲ８４８を有効成分として含有するクリームを得る。

製剤例４　油性軟膏

Ｒ８４８（１０ｇ）を精製水（３０ｇ）に溶解させ、ヘキシレングリコール（１２０ｇ）と混合する。これを溶融させた白色ワセリン（７００ｇ）、白色ワックス（８０ｇ）とプロピレングリコールステアレート（２０ｇ）の混合物に添加し、温度を下げながら均質に撹拌してＲ８４８を有効成分として含有する軟膏を得る。

実施例１

アラキドン酸誘発皮内反応に対するＲ８４８の抑制作用

1）ＢＡＬＢ／ｃマウス(雌、6週令)を日本チャールズリバー(神奈川、日本)より購入し、８週令まで予備飼育し使用した。

2）試験薬物：Ｒ８４８（フリー体）

3）Ｒ８４８を秤量後、アセトンに２０ｍｇ／ｍｌと２ｍｇ／ｍｌの濃度に懸濁した。ジエチルエーテル麻酔下でマウス左耳介の表裏に１０μｌずつＲ８４８懸濁液を塗布した(Ｒ８４８投与群)。コントロール群としてアセトンだけを左耳介の表裏に１０μｌずつ塗布したマウスを用意した。

4）アラキドン酸塗布：Ｒ８４８あるいはアセトン塗布４時間後に１０％アラキドン酸(CAYMAN CHEMICAL. Co.、ミシガン、アメリカ)をＲ８４８投与群とコントロール群の左耳介の表裏に１０μｌずつ塗布した。

5）皮内反応の測定：Ｒ８４８あるいはアセトン塗布前(抗原惹起せず)と１０％アラキドン酸塗布１時間後(抗原惹起したもの)にジエチルエーテル麻酔下でDial Thickness Gage(Mitutoyo Co.、東京、日本)で左右両耳介の厚さを測定した。皮内反応は、(抗原惹起した左耳介の厚さ)－(抗原惹起しない右耳介の厚さ)で表現した。

6)解析：スチューデントｔ－テスト(Student's t－test)検定で有意差検定を行った。１％以下の危険率で有意差が認められた場合は、ｐ＜０．０１の表示で表した。その結果を表１に示す。

表１．Ｒ８４８のアラキドン酸誘発皮内反応に対する抑制効果

	N	皮内反応（平均値：μm）	ＳＥＭ	有意差検定
対照群	5	２０８．０	１４．６	
R848 (2 mg/ml)	5	６０．０	２３．０	p<0.01
R848 (20mg/ml)	5	６２．０	１３．２	p<0.01

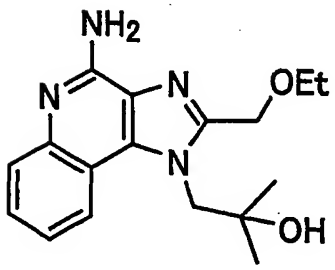
表１から明らかなように、Ｒ８４８（2mg/ml、20mg/ml）は塗布後４時間後においても有意なアラキドン酸誘発皮内反応抑制効果を示した。この結果は、Ｒ８４８含有製剤がアラキドン酸代謝亢進に起因する皮膚疾患の治療剤または予防剤として有効である事を示す。

表２．酸性～中性領域でのＲ８４８およびイミキモドの水溶解度

1ｍｌあたりの最大溶解量（μｇ）			
	ｐＨ ２．５	ｐＨ ５．５	ｐＨ ７．４
イミキモド	３２．４	５０．４	３．４
Ｒ８４８	＞１０００	１０００＞	１０００＞

請求の範囲

1. 下式で表される化合物



（Ｒ８４８：4-アミノ-2-エトキシメチル-α，α-ジメチル-１Ｈ－イミダゾ[4，5－c]キノリン－１－エタノール）またはその酸付加塩または溶媒和物を有効成分として含有するアラキドン酸代謝亢進に起因する皮膚疾患の予防および／または治療のための薬剤。

2. アラキドン酸代謝亢進に起因する皮膚疾患が乾癬、紫外線皮膚炎、肥満細胞症、基底細胞癌または有刺細胞癌である、１に記載の薬剤。

3. 経口投与用剤形である１または２に記載の薬剤。

4. 約１～約１０００ｍｇ／日の投与単位用量のＲ８４８を含有する、３に記載の薬剤。

5. 非経口投与用剤形である１または２に記載の薬剤。

6. 約０．１～約５００ｍｇ／日の投与単位用量のＲ８４８を含有する外用剤である５に記載の薬剤。

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/09575

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07D471/04, A61K31/4745, A61P17/00, 17/02, 17/06, 35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07D471/04, A61K31/4745

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS (STN), REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5389640 A (Minnesota Mining and Manufacturing Company), 14 February, 1995 (14.02.1995), especially, Column 11, lines 58 to 68; Column 35, "EXAMPLE 99" & WO 92/15582 A1 & JP 6-504789 A & AU 2715795 A & HU 67026 A & CA 2104782 A & IE 920605 A & ZA 9201540 A & NO 933069 A & EP 582581 A & NZ 241784 A & CZ 9301788 A & EP 872478 A2	1-6
Y	WO 98/24436 A2 (Minnesota Mining and Manufacturing Company), 11 June, 1998 (11.06.1998), especially, page 1, line 23 to page 2, line 20; page 18, Claim 15 & AU 5368698 A & NO 992638 A & US 5939090 A & CZ 9901955 A & EP 942724 A & BR 9713677 A	1-6

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 January, 2002 (15.01.02)	29 January, 2002 (29.01.02)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/09575

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/40228 A2 (3M INNOVATIVE PROPERTIES COMPANY), 13 July, 2000 (13.07.2000) & AU 2721600 A	1-6
A	WO 98/17279 A1 (Minnesota Mining and Manufacturing Company), 30 April, 1998 (30.04.1998) & AU 5164198 A & NO 991908 A & EP 938315 A & US 6039969 A & HU 9904665 A	1-6

WO 02/36592

[Note: Names, addresses, company names and brand names are translated in the most common manner. Japanese language does not have singular or plural words unless otherwise specified by a numeral prefix or a general form of plurality suffix.]

Description of the Invention

(54) Title: Remedies for Arachironic Acid-Induced Skin Diseases

(57) Abstract:

Drugs for preventing and/or treating arachidonic acid-induced skin diseases, which contain 4-amino-2-ethoxymethyl-α,α dimethyl-1H-imidazo [4, 5-c]quinoline-1-ethanol: R848, or its acid adduct salts or solvates, as their active ingredient. By using these drugs, various skin diseases caused by the accelerated arachidonic metabolism (psoriasis, ultraviolet dermatitis, mastocytoma, basiloma, squamous cell carcinoma, etc.) can be safely and effectively treated.

Description of the Invention

Remedies for Arachironic Acid-Induced Skin Diseases

Technological Field

The present invention is an invention about a skin disease treatment remedies. And then in more details, the present invention is an invention about drugs for preventing and/or treating arachidonic acid-induced skin diseases caused by the accelerated arachidonic metabolism, like psoriasis, ultraviolet dermatitis, mastocytoma, basiloma, squamous cell carcinoma, etc.

Technological Background

The generated through the arachidonic acid induced metabolism conditions prostaglandine (PG) and leucotolyene (LT) are related to physiological function regulation like stomach acid component secretion or blood plate cohesion, different types of smooth muscle contraction etc., and together with that they are fatty acid system information transmission materials (mediators). The PG and the LT are important for the maintenance of the constancy of the living body, and it is considered that in the case of some skin diseases, their excessive generation is the main cause of the disease.

As representative examples of such skin diseases, first, there is the psoriasis disease. The psoriasis is a chronic disease which indicates abnormal benign increase of the front skin cells, and the invasion of multiformity of core white blood cells inside the surface skin, and because of the described here below reasons (1) ~ (4), it is considered that it is a disease related strongly to abnormal products generated by the arachidonic acid

metabolism. (1) In the psoriasis disease skin part, the PG, arachidonic acid and 12-HETE, are increased (Hammerson, S. et al. Proc. Nat. Acad. Sci. USA. 72, 5130-5134 (1975)), (2) if LTB4 is patched onto the human skin, small abscesses inside the surface skin, which look like the psoriasis skin disease parts, are formed (Camp, S. et al. J. Invest. Dermatol. 82, 202 – 204 (1984), (3) through the blood vessel expansion effect of the PG and through the blood vessel permeability acceleration due to the Leucotolyene C, D and E (LTC, LTD, LTE), a skin reddening and swelling reaction, are provoked, (4) through Leucotolyene 5, 12-dihydroxy material (LTB4), the excessive idleness of a large number of white blood cells is increased, and there is a formation of abscesses under and inside an angle layer that is characteristic of psoriasis etc. At the present time, Torechinate (Vitamin A derivative material), active form Vitamin D3, Cyclosporin etc., are used, however, effective psoriasis disease remedies that have a secondary effect etc., at the surface, are desirable (The newest skin disease remedies '97 ~ '98, p 4 – 7, 106-107).

As representative examples of skin diseases caused by abnormal arachidonic acid metabolism, there are the described here below diseases.

Mastocytoma: It is a condition where histamine etc., is released from the increased in the skin mastocystoma, and skin flushing and pale measles are presented. It is considered that these symptoms are mainly caused by the histamine, and because of that antihystamine drugs are used. However, if an agent hindering the PG synthesis is imparted, cases of histamine resistance where a significant improvement can be seen are known (Main, R. A. et al. Br. J. Dermatol. 107 (Suppl. 22) 53 (1982)) and PGD2 excessive generation, are known (Roberts, L. J. et al. N. Engl. J. Med. 303, 1400 – 1404 (1980)).

Sunlight dermatitis: It is considered that the caused by the medium wavelength ultraviolet rays PG etc., inflammation mediators provoke the expansion of the blood vessels.

Basiloma and squamous cell carcinoma (both skin cancers): It is suggested that the PG is increased and the PG participates in the increase of these tumors (Vanderveen, E. E. et al. Arch. Dermatol. 122, 407-412 (1986)).

On the other hand, the 4-amino-2-ethoxymethyl -α, α - dimethyl – 1H – imidazo [4, 5-c] quinoline – 1- ethanol (R848), is a compound that is known to have the described here below pharmacological effects.

1) The antiviral effect: The antiviral effect in a herpes virus infected system has been reported (Tomai, MA. Et al. Antiviral Res. 28, 253-264 (1995)).
2) Citokine inducement effect: The fact that the generation of IFN, intaloikin type (IL-1, IL-6, IL-8) or tumor destruction death causing element α (TNF-α) causes the inducement, has been reported (Wagner et al. Cytokine 9 837-845 (1997)).

Regarding R848 and 1-(2-methylpropyl) –1H-imidazo[4, 5-c]quinoline-4-amine (imichimodo), the appropriate use of treatment of allergic skin inflammation by the advantageous use of the Th2 type cytokine generation hindrance effect, is well known (WO 98/17279). Also, regarding the imichimodo, a patent application has been filed by

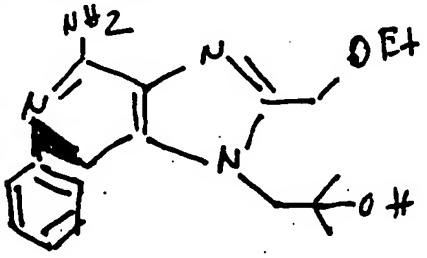
the authors of the present invention regarding its appropriate use for skin diseases that are caused by abnormal arachidonic acid metabolism (Japanese Patent Application Number Hei-Sei 2000-247884). However, in the previously described preceding technical references there has been no reporting whatsoever relative to an indication that the R848 has any prevention and/or treatment effect on skin diseases induced by abnormal arachidonic acid metabolism. Rather, except for the imichimodo, the TNF-α production inducing effect that has been recognized only in the R848 (Wagner et al. Cytokine 9 837-845 (1997)) has been combined with the TNF-α skin inflammation provocation effect (Kondo, S et al. Eur. J. Immunol. 27, 1713-8 (1997)), and it indicates the possibility of the R848 skin inflammation provocation.

Invention Description

The problem of the present invention is to suggest a novel skin disease treatment agent (remedy) for the treatment and/or the prevention of skin diseases caused by accelerated arachidonic acid metabolism, namely, skin diseases caused by the accelerated production of PG, LT etc.

The authors of the present invention have already observed the suppression effect of the imnichimodo on the swelling of the mouse ear induced by arachidonic acid, and a patent application for an invention for skin disease remedy for psoriasis, etc. has been filed (Japanese Patent Application 2000-247884, previously issued). However, at this time, it has been discovered that the imichimodo type afforestation compound R848 is a material that shows an effect of suppressing the swelling of mouse ear induced by arachidonic acid, which has extremely strong persistence, and by that the present invention has been accomplished. Namely, the essential elements of the present invention are shown in the described here below [1] ~ [6].

[1] Drugs for preventing and/or treating skin diseases induced by the accelerated metabolism of arachidonic, which contain a compound with the described here below formula



(4- amino-2-ethoxymethyl-α,α-dimethyl-1H-imidazo [4, 5c]quinoline-1-ethanol, here below called R848) or its acid adduct salts or solvates, as their active ingredient.

[2] Drug according to the above described [1], where the skin disease induced by the accelerated metabolism of the arachidonic acid are psoriasis, ultraviolet dermatitis, mastocytoma, basiloma or squamous cell carcinoma.

[3] Drug according to the above described [1] or [2] where it is a drug form, which is orally received.

[4] Drug according to the above described [3] where it contains approximately 0.1 ~ approximately 1000 mg/day imparted units amount of R848.

[5] Drug according to the above described [1] or [2] where it is a drug form, which is not orally received.

[6] Drug according to the above described [5] where it is an external use drug, which contains approximately 0.1 ~ approximately 50 mg/day imparted units amount of R848.

According to the present invention, the term "skin diseases induced by the accelerated metabolism of arachidonic acid" has the meaning of skin diseases generated by the abnormal increase of the arachidonic acid, which forms the structure of the arachidonic acid metabolism circumstances (arachidonic acid cascade) and its metabolism materials, and in more details, they are psoriasis, ultraviolet dermatitis, mastocytoma, basiloma, squamous cell carcinoma, etc. Regarding the arachidonic acid metabolism materials, this means (1) the generated by cyclooxygenaze enzyme prostaglandine type: PGE (prostaglandine E), PGF, PGI, TXA (tromboxane A), etc., (2) the produced by the lipoxygenaze enzyme leucotolyene type: LTB4, LTC, LTD, LTE etc., and (3) 12-HETE, etc., and the inflammation skin diseases that are caused as a result from the abnormal increase of these mediators, are the subject of use of the present invention.

However, in the skin diseases according to the present invention, the virus or bacteria infection diseases, burn and freeze wounds, skin inflammation symptoms caused by external wounds, skin diseases accompanying glue originating diseases (full body eritematodes, strong skin diseases, etc., autoimmune diseases), allergic skin diseases generated through unusual immune reaction (hives, contact skin inflammation, atopi skin inflammation etc.) are not included.

Here below the active ingredients according to the present invention and their manufacturing method, will be described.

The R848 and its acid adduct salts, which constitute the active ingredients of the present invention are materials that can be easily synthesized according to well known methods. For example, it is a good option if the method references according to the reported in the WO 98/17279, is used. As the acids of the acid adduct salts of R848, there are no particular limitations as long as they are acids that are pharmaceutically allowed, and it is also a good option if they are solvates of water etc. Regarding the acid adduct salts, they are formed by using inorganic acids (for example, hydrochloric acid, bromic acid, sulfuric acid, phosphoric acid and nitric acid, etc.), or acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, arginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalene disulphonic acid, and polygalacturonic acid, etc., organic acids. The slats from the hydrochloric acid,

sulfuric acid, acetic acid, oxalic acid, ascorbic acid etc., are the preferred acid adduct salts.

The R848 and its salts are obtained and sold in different manufactured agent conditions (for example, liquid agent, sold phase agent, capsule agent etc.). As an agent form in order to be used for oral administration, for example, there are the pill agent, capsule agent, spherical agent, particular agent, dispersed agent, liquid agent, suspended agent, etc., forms. And as agent forms for non-oral type administration, for example, there are the aqueous agent or oil type agent used for injections, the soft ointment agent, the cream agent, the lotion agent, the aerosol agent, the suppository, the adhered (patch) agent, etc.

Also, it is possible to admix and use other active ingredients as long as they do not deteriorate the desired effect, or it is possible to admix and use antibiotic materials, antibacterial agents, other anti-inflammation agents or antiviral compounds, etc., that promote the desired effect.

With the goal of oral medical treatment administration, it is possible that the active ingredient is incorporated and combined into an allotment agent, and it is used as a liquid agent, powder agent, dispersed agent, pill agent, torochi agent or capsule agent. It is also possible that a binding agent and/or an adjuvent agent, which are pharmaceutically compatible are contained as one part of the composition material. Regarding the pill agent, the spherical agent, the capsule or the torochi etc., it is also possible that they include a component or compound that is similar to the listed below materials: microcrystalline cellulose, gamutoragacanto or gelatine, etc., binding agents; starch powder or lactose, etc., allotment type agents; arginic acid, rimogel or corn starch etc., dispersing agents; magnesium stearate or Sterotes etc., lubricating agents; colloidal type silicon dioxide etc., slip agents, sucrose or saccharine etc., sweetening ingredients; or peppermint, methyl salicilate or orange flavoring agent, etc., flavoring agents. In the case when the administered unit state is a capsule state, in addition to the above-described types of materials, it is also possible to include an aliphatic oil type liquid material carrier. Then, regarding the administered unit state, in order to improve the physical condition of the administered unit, it is possible to include different types of other materials, for example, a sugar cover layer, shellac or a agents soluble in the digestive tract. The R848 and the pharmacologically allowed salts can be administered as components of elixirs, suspensions, syrups, or chewing gum etc. Regarding the syrups, in addition to the active ingredient as a sweetening agents, they include sucrose, and specific preservatives, dyeing materials, and coloring agents and together with that flavoring agents.

Also, the R848 is manufactured and sold as a slow release manufactured agent including a skin grafting and microcapsule administration system. As the carrier materials, it is possible to use vinyl ethylene acetate, polyanhydrides, polyglycolic acids, collagen, silicone, polyorthoesters and polylactic acid etc., biodegradable polymers that are useful for the living matter. Regarding the manufacturing method for the preparation of such manufactured agents, it is clear to people skilled in the industry, and the materials also can be procured as commercially available products. Also, it is possible to be

manufactured according to the method that is known to people skilled in the industry where a liposome suspension liquid suitable fatty material (for example, stearoyl phosphatidyl ethanolamine, stearoyl phophatidyl chloine, aracadoyl phosphatidyl chloine, and cholesterol) are used as the carrier material.

In the solution or suspension, which contains R848 as its active ingredient and is used for non-oral administration, in the skin, under the skin or for local application, it is possible to include the described here below components. Water used for injections, salt water solution, fixedoil, polyethylene glycol, glycerine, propylene glycol or other synthetic solvents, etc., disinfection dilution agents; benzyl alcohol or methyl paraben etc., disinfection agents; ascorbic acid or sodium sulfonate etc., anti-oxidation agents; ethylene diamine tetra acetate etc., chelating agents; acetate, citric acid or phosphoric acid etc., buffering agents and sodium chloride or dextrose etc., chemicals used for regulating the degree of extension. The non-oral manufactured agents are obtained as they are sealed into ampules, disposable injection vessels, or glass or plastic manufactured repeat administration doses vials. The injection agents can be manufactured according to the usual methods, for example, the above compounds are dissolved in an appropriate solvent (for example, sterile water, buffer solution, physiological salt water solution, etc.) and after that, they are filtered through a filter and sterilized, and then next, they are filled into sterile (non-bacterial) containers. In the case when these are administered inside the vein, the preferred carrier is physiological, salt-water solution or phosphoric acid buffer table salt solution (PBS).

According to the present invention, the external application agent is especially appropriate agent form. Regarding the R848, compared to the imichimode, which has a similar chemical structure, 1-(2-methylpropyl) –1H-imidazo [4, 5-c] chinoline – 4-amine, it has characteristic properties where it is said that its water solubility is at least 20 times higher (at pH 2.5, 5.5 and 7, water solution concentration of at least 1000 micrograms/ml or higher). Because of this property, the drug according to the present invention can be easily manufactured, and not only that, but also, the transfer of the active ingredient towards the center or other structures (anatomical) is low. Also, the effect on the afflicted part is sustainable. As described above, the manufactured agent containing the R848 according to the present invention is a material that is especially excellent as an external application agent.

There are no specific limitations regarding the agent form of the external application agent, and there are the materials that are made into a cream form, paste form, jelly form, gel form, emulsion form, solution form, etc., (soft ointment agent, riniment agent, lotion agent etc.), the materials where the material obtained as the medicine and the skin absorption acceleration agent, are dissolved or mixed and dispersed, is spread over the supporting material (cataplasm, etc.), the materials obtained as the above described medicine and skin absorption acceleration agent (the application in the case of the invention claim 3 of the present invention) are dissolved or mixed and dispersed into an adhesive agent, and this is then spread on the surface of the supporting (carrier) material (plaster agents, tape agents, etc.), etc. As the substrates that are used as the above described substrate agents they are good option as long as they are pharmacologically

allowed, and as the substrate agents for the soft ointment agents, riniment, lotion etc., it is possible to use the materials that are well-known from the previous technology, for example, sodium arginate, gelatin, corn starch, toragant gum, methyl cellulose, hycroxy ethyl cellulose, carboxy methyl cellulose, xatance gum, dextrin, carboxy methyl starch, polyvinyl alcohol, sodium polyacrylate, methoxy ethylene – maleic acid anhydride copolymer material, polyvinyl ether, polyvinyl pyrolidone, etc., polymers; natural wax, olive oil, cocoa oil, sesame oil, soybean oil, camellia oil, peanut oil, beef tallow, lard, lanoline etc., fatty type matter; white color Vaseline, yellow color Vaseline; paraffin; hydrocarbon gel soft ointment (for example, product with the trade name of Plastibase, manufactured by Shosei Pharmaceutical Company); stearic acid etc., high homologous order aliphatic acids; cetyl alcohol, stearyl alcohol, etc., high homologous order alcohols; polyethylene glycol; water etc. Then, depending on the requirements, it is also a good option if kaolin, bentonite, zinc oxide, titanium oxide etc., inorganic filler agents; viscosity regulating agents, anti-ageing agents, pH regulating agents, glycerine, propylene glycol etc., moisture preserving agents, etc., are added.

In the case of the external use substrate agent (soft ointment, cream etc.), usually, relative to 1 gram of the ointment material, in the range of 1 ~ 1000 mg, and preferably, in the range of 3 ~ 300 mg of R848 or its salts, are contained as the active ingredients.

Regarding the drug according to the present invention, there are no particular limitations relative to the administration state or the administered amount, and it is a good option as long as it is used according to the methods applied by the persons skilled in the industry, however, the described here below methods can be shown as examples.

Namely, in the case of oral administration, it is possible to be administered as an inhalation agent or a capsule agent, a pill agent, a powder agent etc., agent form, and usually, in the case of oral administration, it is administered for adults daily in the range of approximately 1 ~ approximately 1000 mg, and preferably in the range of approximately 10 ~ approximately 500 mg, at one time or divided in several times.

In the case of non-oral administration, it is possible to use as an aqueous suspension under the skin or as a venous injection agent, a dripping agent, or a soft ointment etc., agent forms. In the case of injection agent, the dosage amount varies depending on the patient symptoms, age, body weight, etc., and also, even though an appropriate amount is applied so that it is sufficient for the effective treatment of the symptoms of the patient, it can be administered in an amount in the range of approximately 0.1 ~ approximately 500 mg, and preferably, in an amount that is in the range of approximately 3 ~ approximately 100 mg, at one time, or divided into several times. In the case of external use skin application manufactured agent (liquid agent, oily soft ointment, hydrophilic soft ointment or cream), the used amount varies depending on the type of the disease and the degree of the symptoms, the size of the affected part, etc., however, as the amount of the external use agent, daily, it is a good option if it is appropriately used on the diseased part in an amount that is in the range of 0.1 ~ 100 g, and then more preferably, in the range of 1 ~ 10 grams, at one time, or separated in several times.

Technological Sphere of Advantageous Application

According to the present invention, it is possible to safely and also effectively treat different types of skin diseases caused by the abnormal arachidonic metabolism (psoriasis, ultraviolet dermatitis, mastocytoma, basiloma, squamous cell carcinoma, etc.).

Practical Examples

Here below, practical application examples are presented and the present invention is described in further details, however, the present invention is by no means limited by these practical application examples.

Manufactured Agent Example 1

Solution agent used for injections

In purified water (2 ml), R848 (200 mg) and erithritol (250 mg) are dissolved, and by that a non-oral administration solution agent is manufactured.

Manufactured Agent Example 2

Solution agent used for oral administration

In purified water (1 ml), R848 (200 mg) and glycerine (200 mg), citric acid (6 mg) and sodium citrate (20 mg) are dissolved and by that an oral administration type liquid agent is manufactured.

Manufactured Agent Example 3

Cream

In the R848 (2 g), 5 grams of crotamiton, 5 grams of niccol (TS-10), 3 grams of liquid paraffin, and 15 grams of isopropyl myristate, are added, and this is heated to a temperature of 70oC, and dissolved. To that material, a solution obtained as 1 gram of carboxy vinyl polymer has been allowed to swell in 60 grams of water, is added, and it is emulsified while stirring. After that, a solution obtained as 0.5 grams of diisopropanol amine was dissolved in 9.75 grams of water, was added and it was stirred until the material became homogeneous, and a cream, containing R848 as its active ingredient, was obtained.

Manufactured Agent Example 4

Oily soft ointment

R848 (10 grams) were dissolved into purified water (30 grams), and this was mixed with hexylene glycol (120 grams). This was added to a mixture of molten, white color

glycerine (700 grams), white color wax (80 grams), and propylene glycol stearate (20 grams), and as the temperature was decreased it was stirred into a homogeneous material, by that a soft ointment containing R848 as its active ingredient, was obtained.

Practical Implementation Example 1

R848 suppressing action relative to arachidonic acid provoked reaction inside the skin

1) BALB/c mouse (female, 6 weeks old) was purchased from Nippon Charles River (Shinakawa, Japan), and it was prepared and raised until it was 8 weeks old, and it was then used.
2) Experimental medicine: R848 (cream material)
3) The R848 was weighted and after that it was suspended in acetone so that the concentrations became concentrations of 20 mg/ml and 2 mg/ml. Under diethyl ether anesthesia, on the front and the back of the left ear of the mouse, 10 microliters each of the R848 suspension was coated (R848 administration group). As the control group, mouse was used where only acetone was used and that was applied on the front and the back of the left ear at an amount of 10 microliters each.
4) Arachidonic acid application: 4 hours after the application of the R848 or the acetone, 10 % arachidonic acid (CAYMAN CHEMICAL CO., Michigan, USA), was applied on the front and back of the left ear of the R848 administered group and the control group, at 10 microliters each.
5) Measurement of the reaction inside the skin: Prior to the application of the R848 or the acetone (without provoking an antigen) and one after the application of the 10 % arachidonic acid (after the provocation of the antigen) under diethyl ether anesthesia, the thickness of both the right and the left ears was measured by using a Dial Thickness Gage (manufactured by Mitutoyo Co., Tokyo, Japan). The reaction inside the skin was expressed as the (thickness of the antigen provoked left ear) – (thickness of the non-antigen provoked right ear).
6) Analysis: According to the Student's t-test inspection, the inspection for intentional differences was conducted. In the case when the intentional difference was observed at no more than 1 % or less risk ratio, it was represented by an indication of $p<0.01$. The results from this analysis are presented in Table 1.

Table 1. Suppression effect of R848 on the arachidonic acid induced reaction inside the skin

	N	Reaction inside the skin (average value: microns)	SEM	Intentional difference inspection
Comparison Group	5	208.0	14.6	
R848 (2 mg/ml)	5	60.0	23.0	P<0.01
R848 (20 mg/ml)	5	62.0	13.2	P<0.01

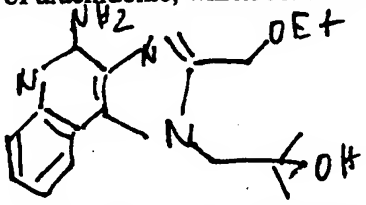
As it is clear from the table here above, in the case of the R848 (2 mg/ml, 20 mg/ml), even after 4 hours after the application, an intentional suppression effect on the arachidonic acid induced reaction inside the skin, was observed. This results shows that the R848 containing manufactured agent is effective as a treating agent or as a prevention agent relative to skin diseases induced by the accelerated metabolism of arachidonic acid.

Table 2. Water solubility of R848 and imichimodo in acidic ~ neutral ranges

Maximum dissolved amount (micrograms) in 1 ml			
	pH 2.5	pH 5.5	pH 7.4
Imichimodo	32.4	50.4	3.4
R848	>1000	1000>	1000>

Range of the Claims

1. Drug for preventing and/or treating skin diseases induced by the accelerated metabolism of arachidonic, which contain a compound with the described here below formula



(R848: 4- amino-2-ethoxymethyl-α,α-dimethyl-1H-imidazo [4, 5c]quinoline-1-ethanol, here below called R848) or its acid adduct salts or solvates, as their active ingredient.

2. Drug according to the above described [1], where the skin disease induced by the accelerated metabolism of the arachidonic acid are psoriasis, ultraviolet dermatitis, mastocytoma, basiloma or squamous cell carcinoma.

3. Drug according to the above described [1] or [2] where it is a drug form, which is orally received.

4. Drug according to the above described [3] where it contains approximately 0.1 ~ approximately 1000 mg/day imparted units amount of R848.

5. Drug according to the above described [1] or [2] where it is a drug form, which is not orally received.

6. Drug according to the above described [5] where it is an external use drug, which contains approximately 0.1 ~ approximately 50 mg/day imparted units amount of R848.

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08/19/02